Synthetic studies of the zaragozic acids/squalestatins

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Synthetic Studies of the Zaragozic Acids / Squalestatins

Submitted by Paul Andrew Barsanti
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To my family for their constant love, support and belief, but especially to my father, without whom my eyes would never have been opened to the fascinating world of science

Abstract

This thesis is divided into four Chapters. The first Chapter begins with a brief introduction to the area of coronary heart disease and hypercholesterolemia prior to an overview of the isolation, structure determination and biological properties of the zaragozic acids/squalestatins. Following a review of model core syntheses, followed by total syntheses, of the zaragozic acids, our retrosynthetic analysis is given.

The second Chapter describes the successful synthesis of a model core system of the zaragozic acids. Stille coupling methodology, followed by use of a double Sharpless asymmetric dihydroxylation to incorporate four contiguous stereocentres, and elaboration to the model bicyclic core is reported.

Chapter Three describes our attempts to elaborate the synthesis toward a total synthesis of zaragozic acid D. The preparation of the C1 sidechain, and its attempted coupling to a key aldehyde are reported.

The fourth Chapter provides a formal account of experiments and procedures.

Contents

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I am greatly indebted to my supervisor, Dr. Alan Armstrong, for his enthusiasm, encouragement, guidance and friendship over the past three years. I would also like to thank my colleagues, both past and present, for creating an enjoyable working environment. Particular thanks to Dr. Doug Critcher and Lyn Jones, not only for their exceedingly speedy and careful proof-reading of this thesis, but also for their friendship and chemical advice.

This work would not have been possible without the assistance of the technical staff of both Bath and Nottingham Universities. Special thanks are due to Dr. Dick Kinsman (Bath) and Dave Wood (Bath) for always being willing to help with nmr work. Thanks also to Dr. J.A. Ballantine and his staff at the EPSRC Mass Spectrometry Service in Swansea.

Last, and by no means least, I would like to thank Gail for her constant love and support, and for keeping me going.

Abbreviations

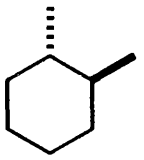
Ac	Acetyl
AD	Asymmetric *cis*-Dihydroxylation
AIBN	α, α'-Azoisobutyronitrile
Ar	Aromatic
Bn	Benzyl
Boc	Butoxy carbonyl
br	Broad
Bu	n-Butyl
^{t}Bu	*tert*-Butyl
cat.	Catalytic (amount)
CD	Circular dichroism
CHD	Coronary heart disease
CI	Chemical ionisation
CLB	Chlorobenzoate
CoA	Co-enzyme A
Conc.	Concentration
CSA	Camphorsulfonic acid
d	Doublet
Δ	Heat
dba	Dibenzylideneacetone
DHQ	Dihydroquinine
DHQD	Dihydroquinidine
DIBAL-H	Diisobutylaluminium hydride
DMAP	4-(Dimethylamino)pyridine
DMF	*N*, *N*-Dimethylformamide
DMP	Dess-Martin Periodinane
DTBMS	di-*tert*-Butylmethylsilyl

DMPU	Dimethylpropyleneurea
	[1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone]
ee	Enantiomeric excess
EE	Ethoxyethyl
EI	Electron impact
eq.	Equivalents
Et	Ethyl
Ether	Diethyl ether
FAB	Fast atom bombardment
FCC	Flash column chromatography
h	Hour(s)
$HClO_4$	Perchloric acid
HMBC	Heteronuclear multiple bond correlation spectroscopy
HMG	(S) β-Hydroxy-β-methylglutaryl
HMGR	(S) β-Hydroxy-β-methylglutaryl CoA reductase
HMPA	Hexamethylphosphoramide
Hz	Hertz
IR	Infra red
LDA	Lithium diisopropylamide
LDL	Low-density lipoprotein
m	Multiplet
mins	Minutes
Me	Methyl
MOM	Methoxymethyl
NaHMDS	Sodium hexamethyldisilazide
NMO	*N*-methylmorpholine-*N*-oxide
NMM	*N*-methylmorpholine
NMP	*N*-methylpyrrolidinone
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect

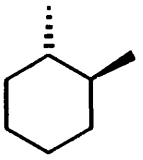
NOESY	Nuclear Overhauser effect correlation spectroscopy
p	para
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
Ph	Phenyl
PMB	*p*-Methoxybenzyl
PPTS	Pyridinium *p*-toluenesulfonate
p-TsOH	*p*-toluenesulfonic acid
Pr	Propyl
Pv	Pivaloyl
q	Quartet
RED-Al™	Sodium bis(2-methoxyethoxy)aluminium hydride
RT	Room temperature
s	Singlet
SAR	Structure activity relationship
SQS	Squalene synthase
t	Triplet
TBS	*tert*-Butyldimethylsilyl
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
Temp.	Temperature
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy, free radical
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyranyl
TLC	Thin layer chromatography
TMEDA	*N, N, N', N'*-Tetramethylethylenediamine
TMS	Trimethylsilyl
Ts	*p*-Toluenesulfonyl

Stereochemical Notation and Compound Numbering

Throughout this thesis, the graphical representation of stereochemistry is in accord with the conventions proposed by Maehr.† Thus, solid and broken wedges denote absolute configuration and solid and broken bold lines denote racemates. For the former, greater narrowing of both solid and broken wedges indicates increasing distance from the viewer.

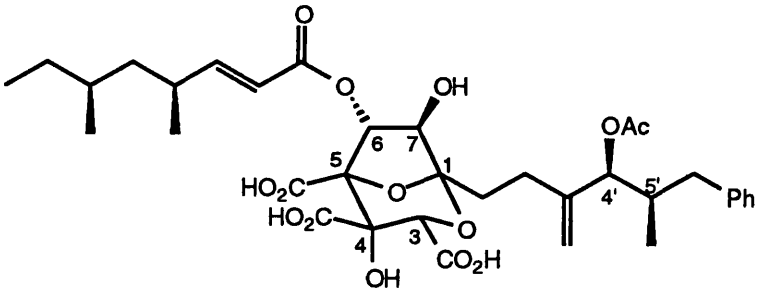


racemic



single enantiomer

In Chapters 1, 2 and 3 of this thesis, the zaragozic acid numbering system shown below is used for all compounds, unless otherwise indicated.



† Maehr, H. *J. Chem. Ed.* **1985**, *62*, 114.

CHAPTER 1

Introduction and review of the Zaragozic acids/Squalestatins

1.1 Coronary Heart Disease

Coronary heart disease (CHD) remains the leading cause of death in the Western world. In fact statistics show that the majority of Western people are more likely to die from cardiovascular diseases each year than from all other diseases combined.

Atherosclerosis is a major risk factor for CHD, and it is now generally accepted that high levels of low density lipoprotein (LDL) cholesterol in the bloodstream, a condition known as hypercholesterolemia, plays a major role in the onset of atherosclerosis. There is a clear connection between the incidence of CHD and hypercholesterolemia. Numerous clinical trials have shown that lowering of serum cholesterol levels by either dietary or pharmacological intervention reduces the incidence of CHD in hypercholesterolemic patients and leads to a significant reduction in deaths from cardiovascular diseases.[1]

Atherosclerosis is a chronic disease in which cholesterol accumulates in the walls of the arteries forming bulky plaques. Over time, these arterial plaques grow and inhibit blood flow. It is a slow process, but ultimately if a blood clot forms and blocks the artery, a heart attack or stroke results which may prove fatal.

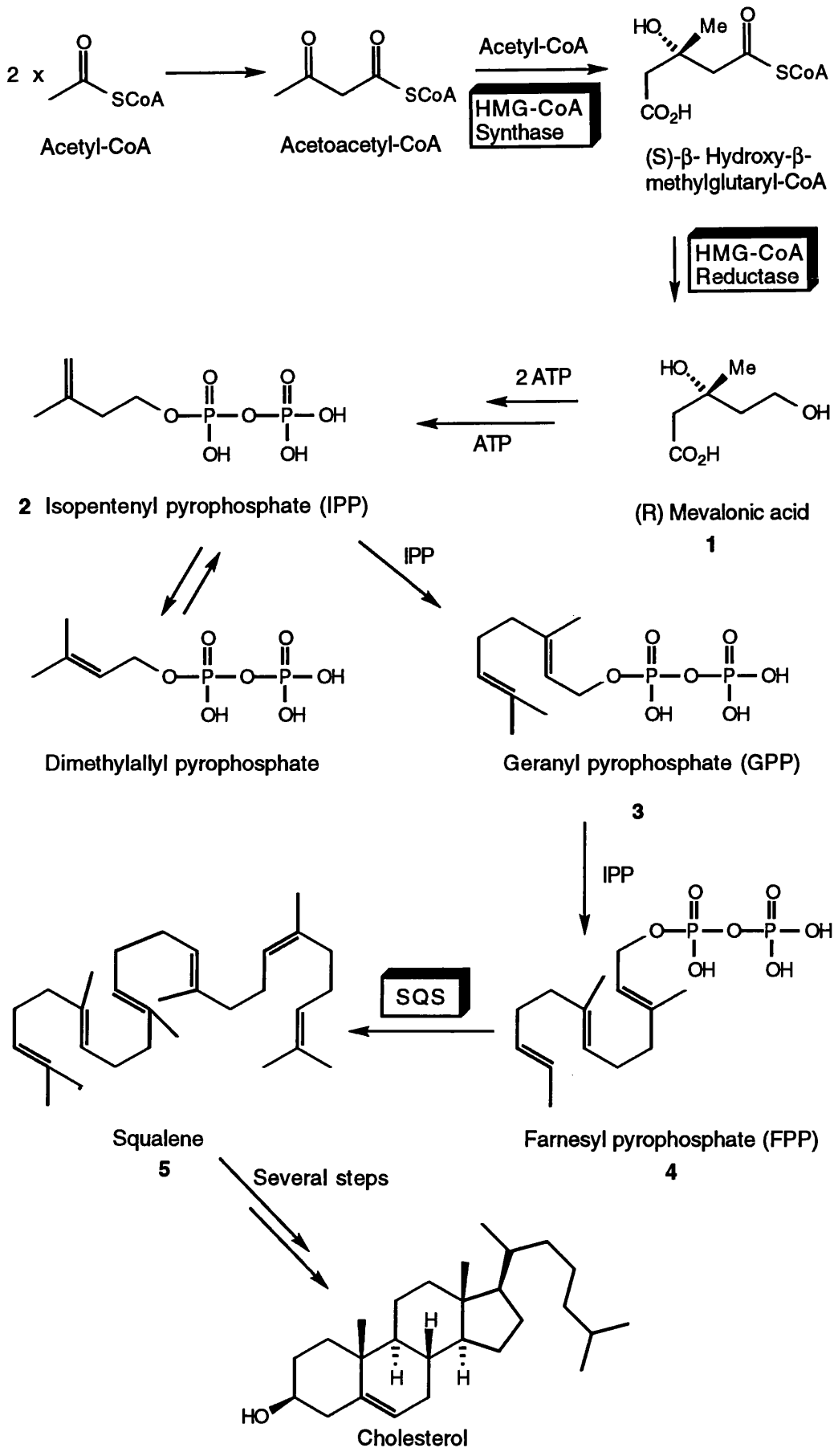
The arterial plaques are believed to be initiated by damage to the thin layer of endothelial cells lining the blood vessels which causes them to become permeable. This allows penetration of the cells by LDL particles and blood platelets. In response to this invasion, smooth-muscle cells in the layer below the endothelium multiply and migrate into the damaged area, along with scavenger cells called macrophages. The smooth muscle cells and the macrophages become foam cells as a response to their ingestion and degradation of the invasive LDL. If high serum levels of LDL are present then LDL cholesterol accumulates in and around the foam cells. This accumulation of cholesterol, cells and debris is what constitutes an atheroma, and the higher the serum levels of LDL, then the more rapid is the onset of the disease.[2]

Therefore, therapeutic intervention by either dietary or pharmacological means, to reduce plasma levels of LDL and hence greatly reduce the rate and extent to which atherosclerosis occurs, has been an area of intensive study.

1.2 Treatment for Hypercholesterolemia

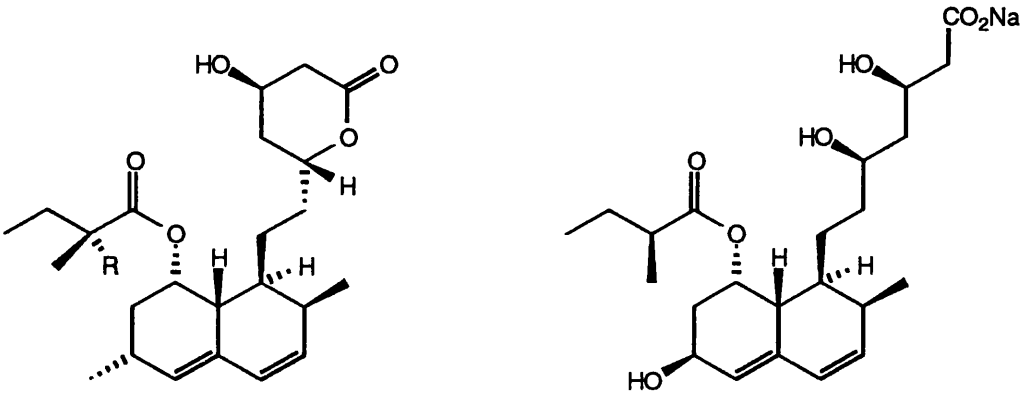
Hypercholesterolemia is a term used to describe the condition of elevated serum cholesterol levels giving rise to a significantly increased risk of CHD. The National Institutes of Health Consensus conference on cholesterol[3] defined plasma levels exceeding 200 mg/dl for 20-29 year olds, 220 mg/dl for 30-39 year olds and 240 mg/dl for 40+ year olds to be moderately hypercholesterolemic. Patients having levels of 20 mg/dl above the moderate cases were deemed as having severe hypercholesterolemia. These differing risk levels require differing levels of treatment in accordance with the severity of the case. In patients where the disease is not in the advanced stages, dietary intervention will play an important role in treatment. High cholesterol diets fill the liver cells with cholesterol and so reduce LDL receptor synthesis, which leads to increased levels of LDL in the blood. Careful control of the dietary intake levels of cholesterol can make considerable reductions in serum cholesterol levels, but in more severe cases, pharmacological intervention is required.

In humans, 70% of total body cholesterol is derived from *de novo* biosynthesis in the liver, and so the inhibition of cholesterol biosynthesis constitutes an important approach to the lowering of elevated serum cholesterol levels. The biosynthetic pathway leading to cholesterol (Scheme 1) commences with self-condensation of acetyl Co-A to give acetoacetyl Co-A, which itself undergoes further condensation with another acetyl Co-A molecule mediated by the enzyme HMG-CoA synthase, to form hydroxymethyl glutaryl-CoA (HMG-CoA). HMG-CoA is then reduced to mevalonic acid **1** by HMG-CoA reductase, and it is this point of the sterol pathway that is believed to be the major rate limiting step. Mevalonic acid **1** is then converted into isopentenyl pyrophosphate (IPP) **2**, which dimerises to give geranyl pyrophosphate (GPP) **3** which in turn joins with another IPP molecule to give farnesyl pyrophosphate (FPP) **4**. Apart from its role in cholesterol biosynthesis, FPP plays a very important role in protein isoprenylation, and is a substrate for both the *cis*- and *trans*-prenyl transferase enzymes, which give rise to very important dolichols and ubiquinone. In the first committed step in the sterol biosynthetic pathway, FPP next undergoes a reductive head to head dimerisation catalysed by the enzyme squalene synthase (SQS), to give squalene **5**, which undergoes a whole series of enzyme mediated reactions which finally lead to cholesterol.



Scheme 1: The biosynthetic pathway leading to cholesterol

Clinical studies have shown reduction in the incidence of cardiovascular mortality from pharmacological intervention, with one such drug, Mevacor (Lovastatin) **6** being one of the pharmaceutical industry's best selling products (Figure 1). The fungal metabolite lovastatin **6**, the microbially transformed product pravastatin **7**, and the semi-synthetic analogue, simvastatin **8**, are potent hypocholesterolemic agents. This class of compound inhibits 3-hydroxy-3-methylglutaryl CoA reductase (HMGR), a major rate limiting enzyme in cholesterol biosynthesis, and has also been shown to induce the expression of hepatic low-density lipoprotein (LDL) receptors which mediate the clearance of LDL cholesterol from the plasma.[4]



R = H ; Lovastatin (Mevacor) **6**
R = Me ; Simvastatin (Zocor) **8**

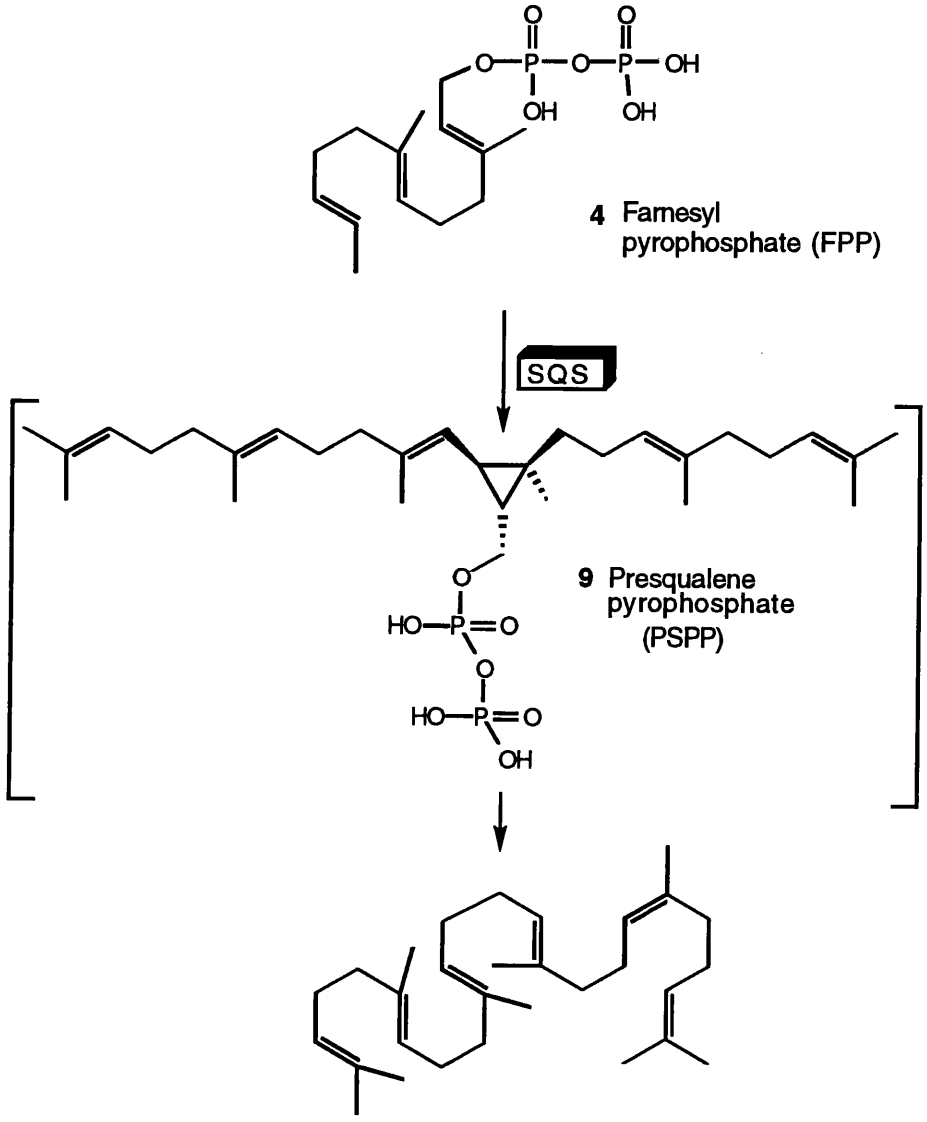
Pravastatin **7**

Figure 1: HMGR inhibitors

However, inhibition of a *branched* biosynthetic pathway at such an early stage can have disadvantages. In this instance, early inhibition puts a block on other important biosynthetic precursors, such as dolichol, ubiquinone, and isopentenyl ^{t}RNA. Furthermore, mevalonic acid **1** is required for production of geranyl pyrophosphate (GPP) **3**, and farnesyl pyrophosphate (FPP) **4**, the terpenoid substrates for protein prenylation. Therefore, pharmaceutical companies have turned their attention to inhibition of enzymes that are unique to the steroid biosynthetic pathway at a later stage.

1.2.1 Squalene Synthase (SQS) inhibitors.

Squalene synthase (SQS) occupies a key branchpoint in the isoprenoid pathway, catalysing the *first committed step* in the biosynthesis of sterols. SQS catalyses the reductive dimerisation of FPP **4** to squalene **5** *via* the intermediate cyclopropane, presqualene pyrophosphate (PSPP) **9** (Scheme 2). Because of its key position in the cholesterol biosynthetic pathway, SQS is an attractive target for pharmacological intervention to reduce serum cholesterol levels.



4 Farnesyl pyrophosphate (FPP)

9 Presqualene pyrophosphate (PSPP)

5 Squalene

Scheme 2

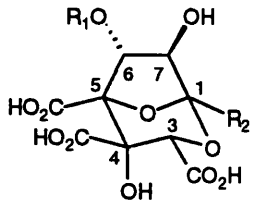
Many inhibitors of SQS have been screened, most of which are based on FPP mimetics and hence contain diphosphate groups which are crucial for substrate binding. However, the activity of this type of compound to date does not offer a useful therapy in the treatment of the disease.

1.3 The Zaragozic Acids and the Squalestatins

In 1992, two independent groups observed high levels of inhibitory activity during screening programmes for inhibitors of SQS. Merck isolated an active component from an unidentified sterile fungal culture isolated from a water sample from the Jalon River in Zaragoza, Spain,[5] whilst Glaxo isolated three active components from a fungus strain *Phoma sp.* C2932 from a soil sample collected at Armacao de Pera, Portugal.[6] Merck designated this new class of compound as the zaragozic acids, and Glaxo named them the squalestatins. Shortly after the initial screening, Merck was to isolate four more fungal metabolites which possessed SQS inhibitory activity. The first of these (zaragozic acid B) was isolated from a *coprophilous* fungus, ATCC 20985, subsequently identified as *Sporormiella intermedia*, which came from cottontail rabbit dung collected near Tucson, AZ.[5] The second (zaragozic acid C) came from a strain of *Leptodontium elatius var. elatius*, ATCC 70411, isolated from wood in the Joyce Kilmer Forest in North Carolina.[7] The last two (zaragozic acid D and D_2) both came from the *keratinophilic* fungus *Amauroascus niger*, ATCC 74156, from forest soil in Los Montes de Poblet, Tarragona, Spain.[8]

Table **1** shows the zaragozic acids and Table **2** shows the squalestatins.

Table 1: The naturally occurring zaragozic acids



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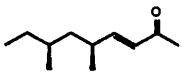
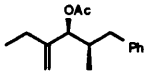
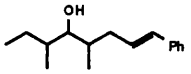
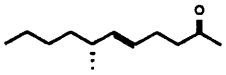
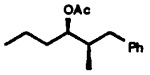
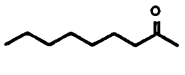
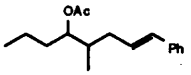
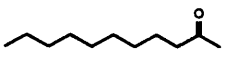
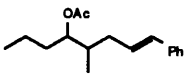
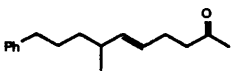
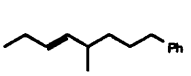
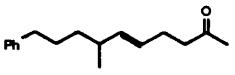
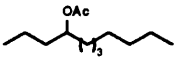
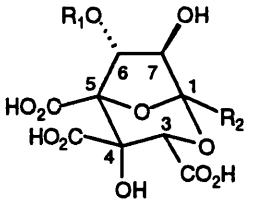
A		
B		
C		
D		
D_2		
E		
F		

Table 2: Selected squalestatins



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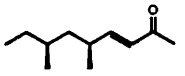
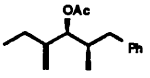
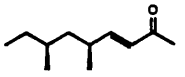
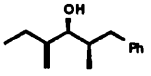
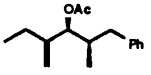
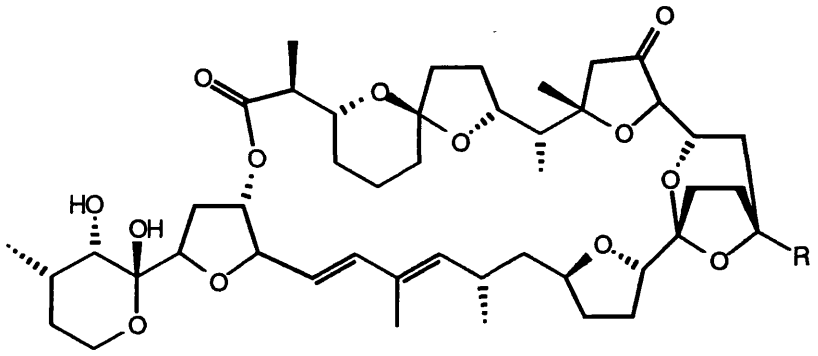
S1		
S2		
H1	H	

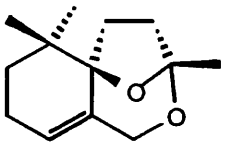
Zaragozic acid A resisted early efforts by Merck workers to obtain it in crystalline form and so the structural assignment was based on advanced 2D-NMR, mass spectrometry and chemical degradation studies.[5, 9, 10] The absolute stereochemistry was obtained from CD experiments. However, unequivocal confirmation was realised afterwards by single crystal X-ray diffraction of a suitable derivative.[10] Likewise, Glaxo carried out extensive 2D-NMR work but were able to get the full relative stereochemistry from single crystal X-ray diffraction of the crystalline S2 tri-methyl ester derivative.[11] The absolute configuration of S1 and S2 was obtained by degradation studies and was found to be [1S (4'S, 5'R), 3S, 4S, 5R, 6R (2"E, 4"S, 6"S), 7R].

Of the 7 zaragozic acids and the majority of the 27 naturally occurring squalestatins, the highly functionalised [1S-(1α, 3α, 4β, 5α, 6α, 7β)]-4, 6, 7-trihydroxy- 2, 8-dioxabicyclo [3.2.1]octane-3, 4, 5-tricarboxylic acid "core" is common to all. Furthermore, these studies showed that zaragozic acid A and squalestatin 1 are identical.

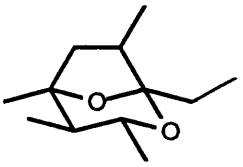
The 2, 8-dioxobicyclo[3.2.1]octane core possessed by all these compounds is rare in nature, and has never been so highly substituted before. It can be found in the shellfish toxins pectenotoxin I, II and III (**10a-c**),[12] the alkaloids daphniphylline[13] and codaphniphylline[14], an ionone **11** isolated from the brandy of quince fruit,[15] and the recently reported[16] banana weevil pheromone sordinin **12**, (Figure 2). The 2,8-dioxobicyclo[3.2.1]octane core has occurred more often in carbohydrate chemistry, particularly as 1,6-anhydrofuranose derivatives,[17] but never as heavily substituted as the zaragozic acids.



10a: R = CH_2OH, pectenotoxin I
10b: R = CH_3, pectenotoxin II
10c: R = CHO, pectenotoxin III



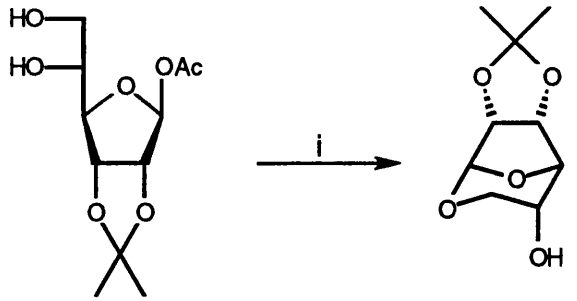
11 ionone



12 sordinin

Figure 2

The 1,6-anhydrofuranoses are commonly prepared *via* an intramolecular acid-catalysed procedure. For example, Lafont and co-workers[18] isolated 1,6-anhydro-2,3-isopropylidene-β-D-allofuranose **13** on heating **14** at reflux with tosic acid in xylene (Scheme 3).

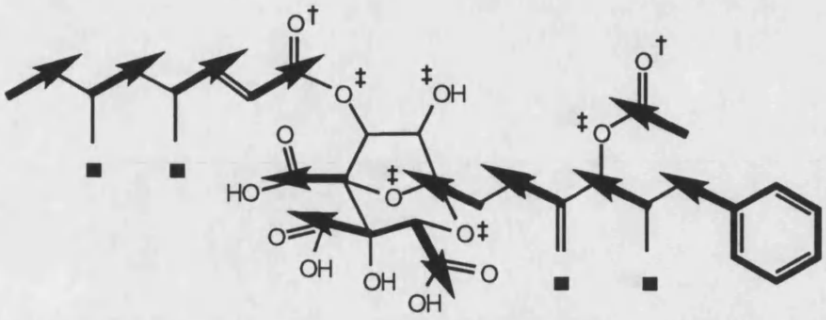


14 **13**

Scheme 3

Reagents and conditions: i) *p*-TsOH, xylene, reflux.

Compounds such as the zaragozic acids raise interesting questions as to their biosynthesis. Zaragozic acid A is derived from two polyketide chains. One chain begins with an aromatic ring derived from benzoic acid, itself derived from phenylalanine, the remaining carbons being derived from a four-carbon unit related to succinate.[19] Feeding studies by Merck with [1-^{13}C] and [1, 2-$^{13}C_2$]acetic acid identified the direction and position of ten acetate units, and showed that the other polyketide chain is formed by condensation of four acetate units and two C-methylations from L-methionine.[19] Glaxo's studies[20] with [1-^{13}C, $^{18}O_2$]acetate and $^{18}O_2$ indicated that five of the oxygens, including both of the heterocyclic oxygens, were derived from atmospheric oxygen, and the oxygens at the two ester carbonyls were derived from acetate (Figure 3).



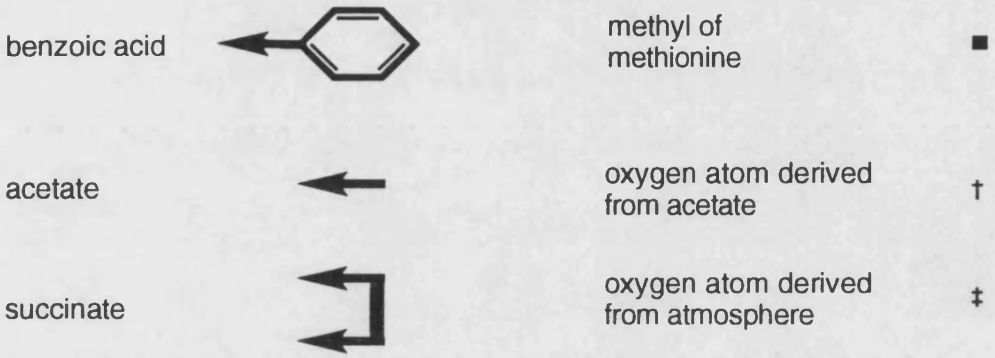
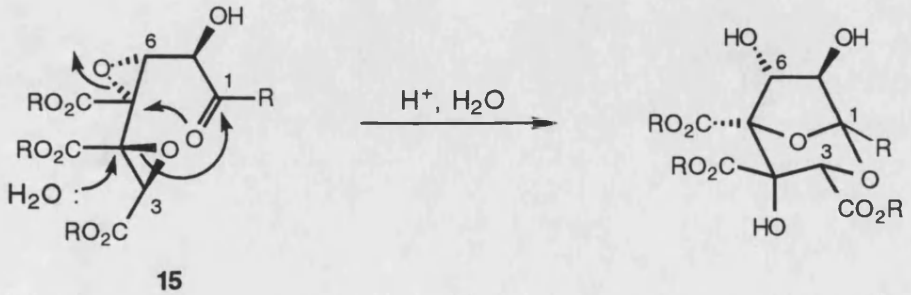


Figure 3: Biosynthesis of zaragozic acid A

However, zaragozic acid F is the first zaragozic acid isolated possessing a non-aromatic terminus of the C1 sidechain,[21] which suggests it is biosynthesised from acetate as a starter unit.

Glaxo[20] have postulated a possible mechanism for the formation of the bicyclic system (Scheme 4). They envisaged the bicyclic core to arise *via* an acid-catalysed tandem cyclisation of the bis-epoxide **15**.



15

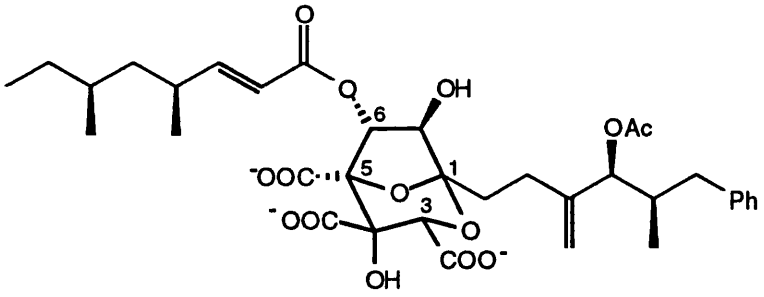
Scheme 4

1.4 Biological Properties of the zaragozic acids

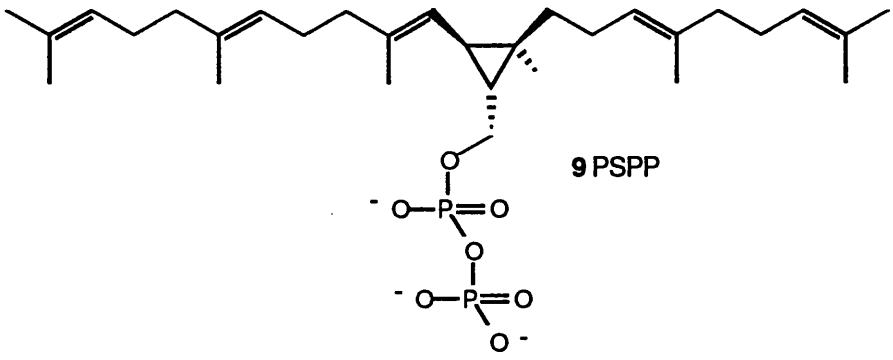
The zaragozic acid/squalestatin family have been shown to be picomolar competitive inhibitors of mouse, rat, and HEPG2 squalene synthase (e.g. zaragozic acid A: $k_i = 78$ pM rat microsomal SQS)[5-8]. This novel class of natural products are 10^3 to 10^6-fold more potent as enzyme inhibitors of SQS than previous SQS inhibitors which have employed pyrophosphate or pyrophosphate analogue containing compounds.

The zaragozic acids / squalestatins have quite a remarkable biological profile as in addition to this very potent SQS inhibitory activity, the family displays broad spectrum antifungal activity against both yeast and filamentous fungi. Also, certain members of the family, in particular, zaragozic acid D and D_2,[8] inhibit the enzyme *ras*-farnesyl-protein transferase (IC_{50} =100 nM), which has implications in the development of anticancer agents, particularly for colon and pancreatic cancer.

It is thought that the zaragozic acids competitively inhibit SQS by mimicking PSPP. Structural similarities can be seen in that they both consist of a polar tri-acid core flanked by two long hydrophobic sidechains (Figure 4).



zaragozic acid A



9 PSPP

Figure 4

Extensive work by both the Merck and Glaxo groups directed towards a better understanding of the structure-activity relationship (SAR) yielded valuable information about the key functional groups essential for activity. It was found that for zaragozic acid A / S1, removal of the C6 acyloxy sidechain resulted in activity approximately equipotent to the parent compound. However, if the sidechain was retained, then modification to it critically influenced the SAR for modifications made elsewhere.

The high potency of zaragozic acid F illustrates that a terminal phenyl group in the C1 sidechain is not required to maintain potent activity.[21] Removal of functionality at C6 and C7 to give the 6,7 di-deoxy analogue,[22] and modification at C3 in the form of the C3 decarboxy,[23, 24] C3 methyl ester,[24] or C3 hydroxymethyl and its derivatives is well tolerated.[25]

The bicyclic core itself is essential, as the monocyclic core analogues containing only the 6-membered ring were orders of magnitude less active.[26] The nature of the tri-carboxylic acid moiety was probed[27, 28] and it was found that the C3 acid is not essential. Esterification of the C3 and C4 acids gave compounds which lacked substantial *in vitro* enzyme inhibitory activity, although the *in vivo* activity was enhanced due to increased bioavailability. However, from all these studies it was apparent that the C5 carboxylic acid must be retained in order to maintain potent activity; modification at this position is not well tolerated by the enzyme.

1.5 Published syntheses of the Zaragozic acids

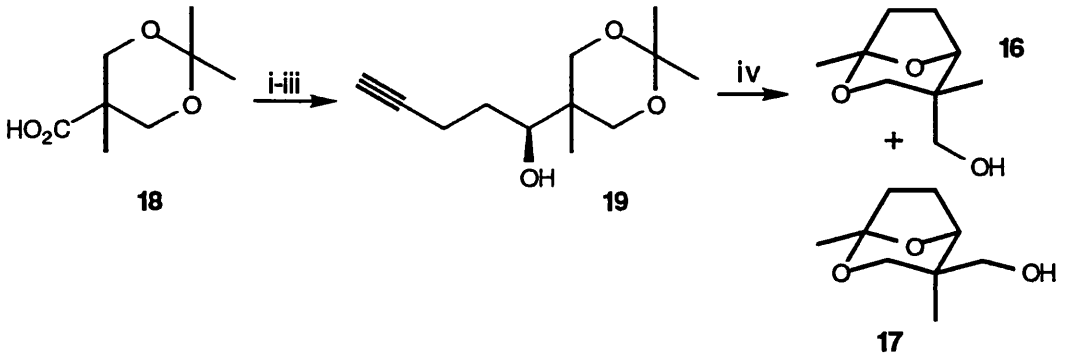
In view of their interesting and potent biological activity along with their remarkable structural features, the zaragozic acids have attracted the attention of the synthetic community.

Before discussing our route to the zaragozic acids, it is worthwhile to examine the strategies developed by other workers.

Initially, attention focused on the synthesis of model core systems with varying degrees of substitution about the 2,8-dioxobicyclo[3.2.1]octane ring. Now, no fewer than four groups have achieved total syntheses of zaragozic acids.[29-34] This Section is divided into two parts. The first part is concerned with approaches to model core systems, and the second part gives an overview of the total syntheses.

1.5.1 Published syntheses of model core systems.

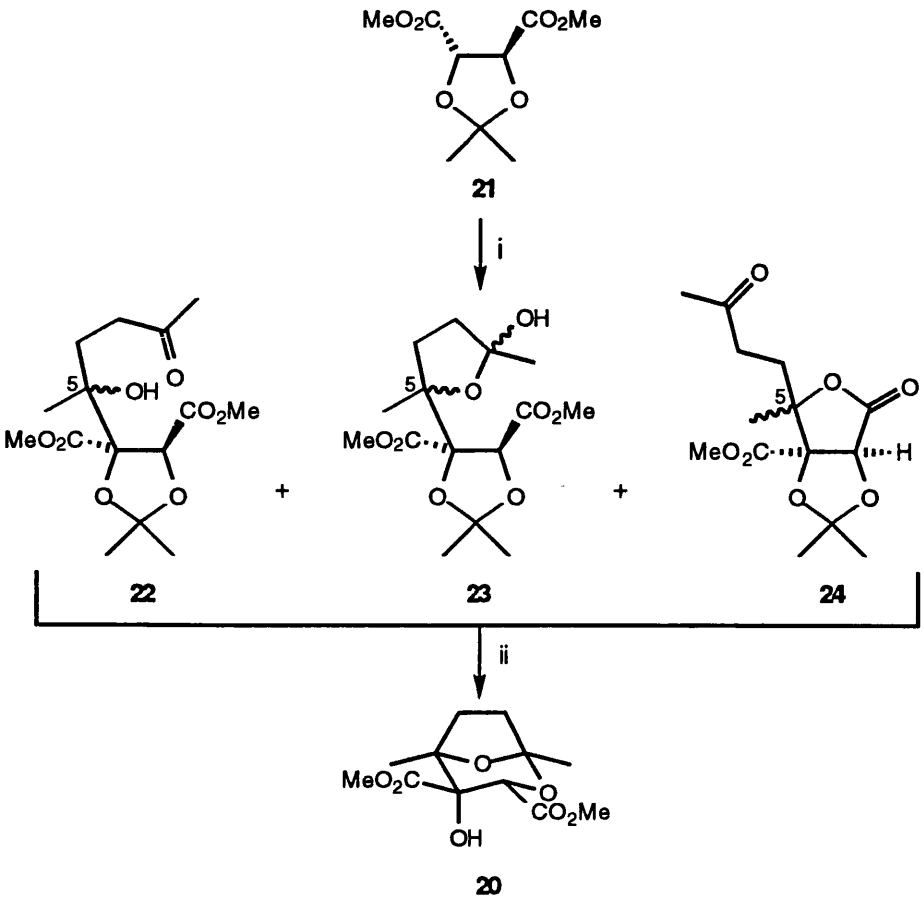
The 2,8-dioxabicyclo[3.2.1]octane ring system had been synthesised prior to the discovery of the zaragozic acids. One such example is the synthesis of the 2,8-dioxabicyclo[3.2.1]octane ring systems **16** and **17**, reported by Heathcock and co-workers[35] as part of the synthesis of the plant alkaloid (-)-secodaphniphylline (Scheme 5). Treatment of the acid **18** with *N*-methoxy-*N*-methylamine, carbonyl diimidazole and then butynyl lithium, followed by reduction of the corresponding ketone and subsequent isomerisation of the alkyne afforded the alcohol **19**. Treatment of **19** with mercuric sulphate and dilute sulfuric acid generated the bicyclic cores **16** and **17** as a 5:1 mixture of diastereoisomers.



Scheme 5

Reagents and conditions: i) MeONHMe, carbonyl diimidazole, CH_2Cl_2, 10 min, then butynyl lithium, THF, 86%; ii) $LiAlH_4$, Darvon alcohol, -80°C, Et_2O, 93%; iii) KH, $H_2N(CH_2)_3NH_2$, -15°C, 45 min, 87%; iv) $HgSO_4$, 1N H_2SO_4, THF, 95%.

The first synthesis of the 2,8-dioxobicyclo[3.2.1]octane ring system directed *specifically* at the zaragozic acids was reported by Aggarwal[36] in 1994 (Scheme 6). Identifying the C3-C4 fragment as an intact tartrate unit, the simple model system **20** was assembled in a two-step procedure. Thus, addition of the lithium enolate of the acetonide **21** derived from (S,S)-dimethyl tartrate, in the presence of 12-crown-4, to acetonylacetone gave a mixture of isomeric adducts. There were at least four isomers present, presumably various diastereoisomers of **22**, **23** and **24**, but it was not possible to determine the relative ratios at this stage. Treatment of the isomeric mixture with HCl in methanol under specific conditions effected cyclisation to give the bicyclic core **20** as a single diastereoisomer.



Scheme 6

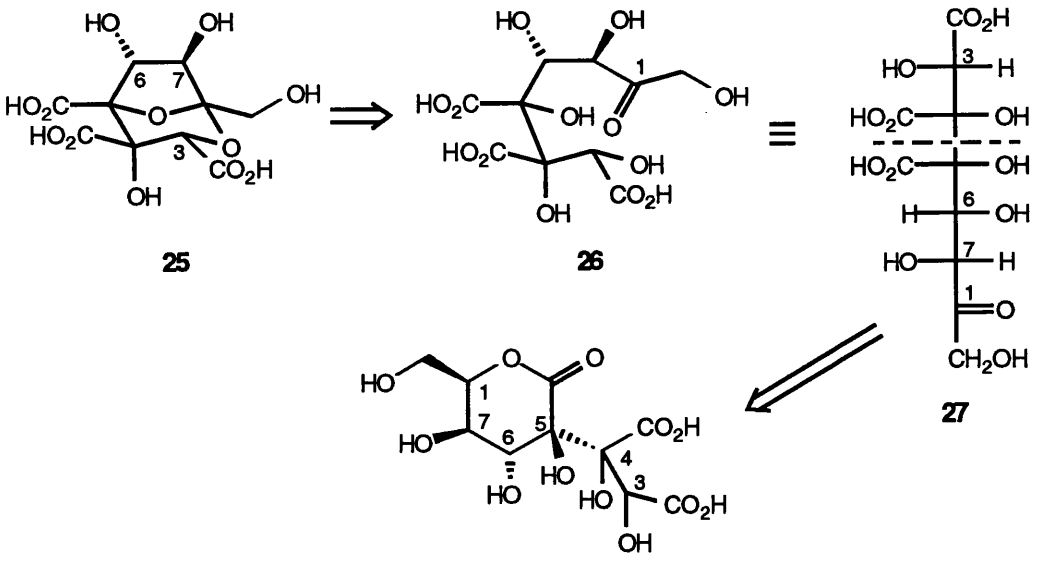
Reagents and conditions: i) acetonylacetone, LDA, THF, 12-Crown-4, -78°C, 5h, 77%; ii) HCl/MeOH, 65°C, 90 min, 30%.

Prolonged heating resulted in lower yields of mixtures of cyclised adducts, presumably arising from the fact that the diastereomer with the wrong stereochemistry at C5 (from the anion addition) is now able to compete in the cyclisation to give less stable core adducts.

This synthesis, though short, suffers from generation of a mixture of isomers. The approach clearly has potential applicability to the real system by use of an appropriately functionalised dicarbonyl compound.

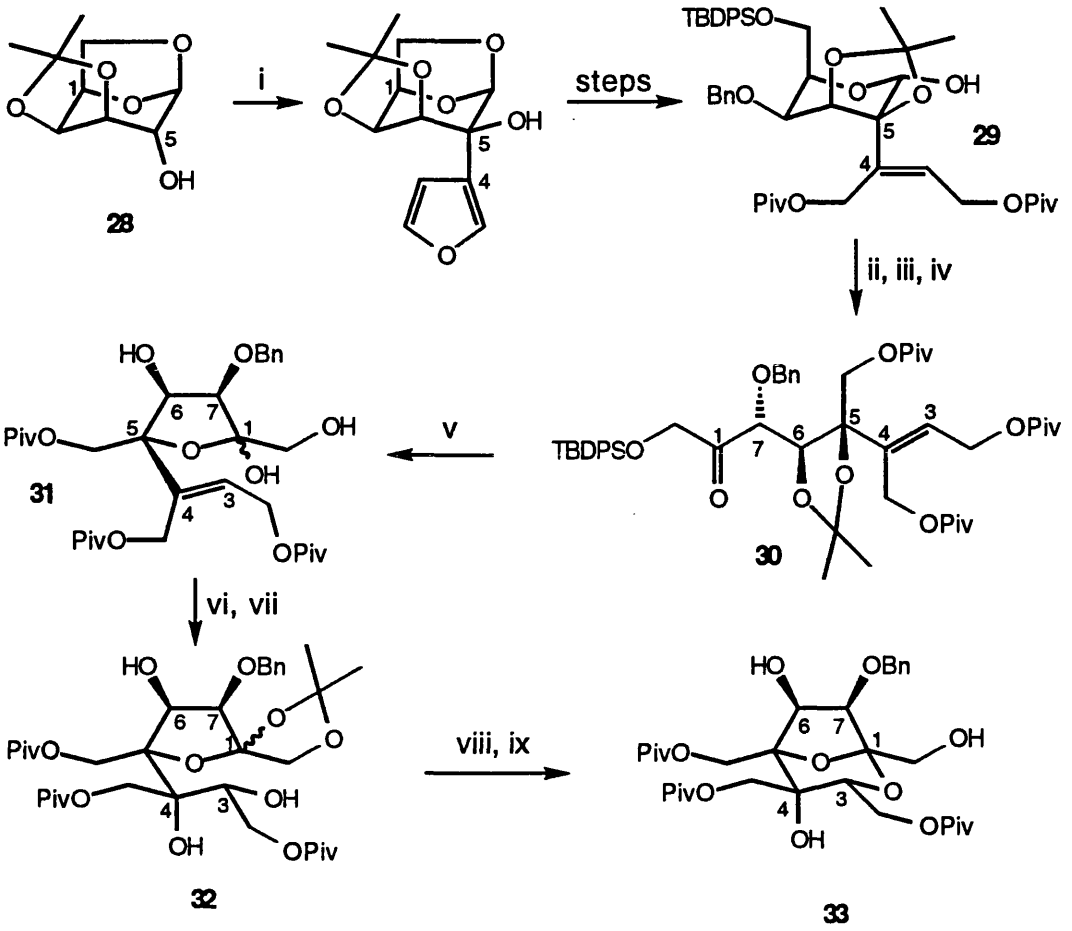
Given the densely oxygenated nature of the bicyclic core, an obvious approach to these systems is the use of carbohydrate precursors. At virtually the same time as the Aggarwal synthesis, the Roberts' group reported the synthesis of a fully functionalised bicyclic core starting from D-galactose.[37] However, their core has the incorrect stereochemistry at C6. Roberts' disconnection of the bicyclic core **25** leads to the hexahydroxyketone **26**, which they envisaged as cyclising to the bicyclic core on treatment with acid. If **26** is written in its Fischer

projection form **27**, then their use of a carbohydrate moiety with a four carbon fragment becomes apparent (Scheme 7).



Scheme 7

Roberts' core synthesis is shown in Scheme 8. Thus, Swern oxidation of **28** followed by addition of 3-lithiofuran as their chosen four carbon fragment occurred exclusively from the α-face. Subsequent manipulations gave the lactol **29** as a single anomer, of which reduction followed by esterification and oxidation gave the ketone **30**. Treatment of **30** with aqueous TFA afforded the furanose **31** as an 8:1 ratio of anomers. Acetonide protection of **31** followed by Sharpless dihydroxylation proceeded stereoselectively to give the triol **32** as a single diastereoisomer which when subjected to acidic conditions cyclised to afford the bicyclic core **33**.

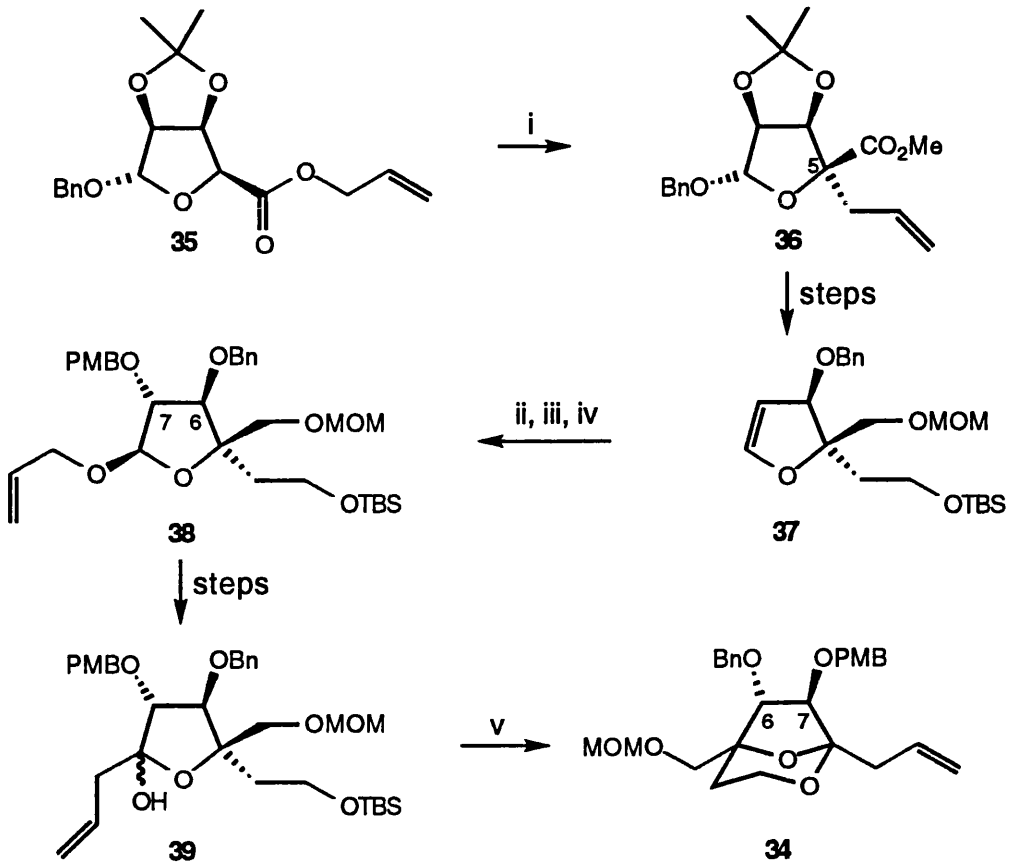


Scheme 8

Reagents and conditions: i) Swern oxidation then 3-lithiofuran, THF, -78°C, 93%; ii) $NaBH_4$, EtOH, 87%; iii) PivCl, pyridine, DMAP, 72%; iv) Jones reagent, acetone, 91%; v) TFA/H_2O (9:1), 0°C, 89%; vi) acetone, anhydrous $CuSO_4$, CSA, 92%; vii) OsO_4, $K_3Fe(CN)_6$, hydroquinidine-4-chlorobenzoate, K_2CO_3, $MeSO_2NH_2$, $^tBuOH/H_2O$ (1:1), RT, 3.5d, 60%; viii) TFA/H_2O/THF (1:1:4), 1d, 60%; ix) CSA, anhydrous $CuSO_4$, CH_2Cl_2, 72h, 41%.

Rizzacasa and co-workers have reported the synthesis of the model core system **34** starting from D-mannose.[38] The key steps involve an Ireland-Claisen rearrangement of the allyl ester **35** and a stereoselective epoxidation of the furanoid glycal **36** with 2,2-dimethyldioxirane. Thus, seven well precedented steps from D-mannose gave the allyl ester **35**, which underwent an Ireland-Claisen rearrangement to give **36**, thereby introducing the C5 carboxyl function. A series of functional group interconversions gave the dihydrofuran **37**, which underwent a stereoselective epoxidation (9:1) with 2,2-dimethyldioxirane resulting in epoxidation from the opposite face to the benzyl ether. Regioselective opening of the resulting epoxide with allyl alcohol, followed by subsequent protection of the C7 hydroxyl as the PMB

ether, gave **38**. Several steps led to the bicyclic precursor **39**, which on treatment with HF/MeCN/H_2O afforded the bicyclic core **34**.



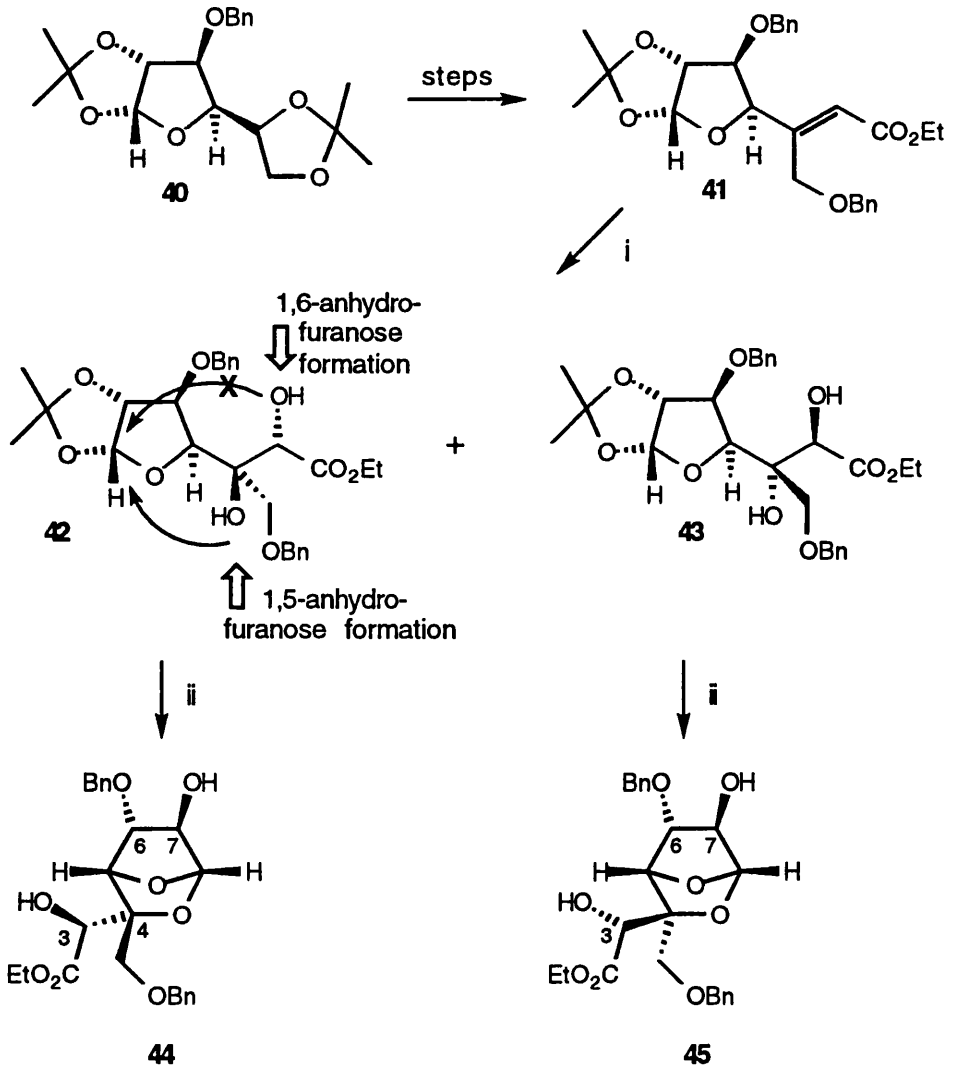
Scheme 9

Reagents and conditions: i) LDA, TMSCl, HMPA/THF, -100°C to RT; CH_2N_2, 71%; ii) 2,2-dimethyldioxirane, acetone, CH_2Cl_2, 0°C; iii) allyl alcohol, RT, 30 mins; iv) PMBCl, NaH, DMF/THF, 84% from **38**; v) 50% HF/MeCN (5:95)/H_2O, RT, 2.5h, 89%.

Gurjar and co-workers have reported some interesting findings in their approach to model core systems.[39] Their work investigated the stereochemical dependence of anhydro-ring formation using carbohydrate templates. Up to three ketal isomers are possible in their systems: 1) a 1,6-anhydrofuranose 2) a 1,5-anhydrofuranose and 3) a 1,6-anhydropyranose. However, their assignments appear to rest purely on 1D-^{1}H NMR shift values and coupling constants. Given the complex nature of the ketal isomers possible, it is difficult to unambiguously rule out other possible ketal isomers for any of the given model cores without full and rigorous 2D-NMR spectroscopy.

Starting from 1,2,5,6-di-*O*-isopropylidene-α-D-glucofuranose derivative **40**, six precedented steps afforded the olefin **41** which when subjected to catalytic osmylation gave a 7:3 diastereomeric mixture of diols **42** and **43** respectively. Both diastereomers gave rise to the 1,5-anhydrofuranoses **44** and **45** upon acid treatment, instead of the desired 1,6-anhydrofuranoses (the latter is the 2,8-dioxabicyclo[3.2.1]octane ring system of the natural product) (Scheme 10).

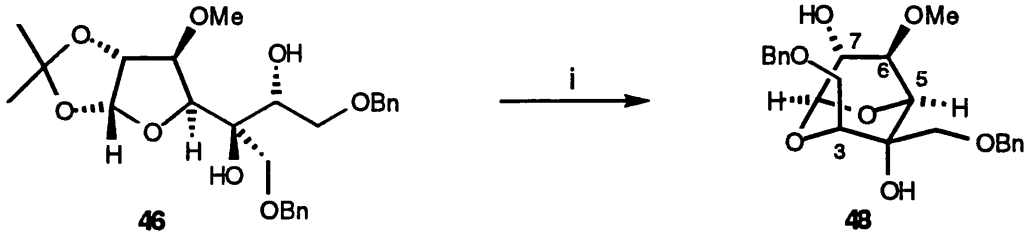
It was thought that generation of the undesired 1,5-anhydrofuranoses could be due to the presence of the carboethoxy group having a diminishing effect on the nucleophilicity of the adjacent hydroxyl group. To test this notion, the ester was reduced to a protected hydroxymethyl group, giving the new cyclisation precursors **46** and **47**.



Scheme 10

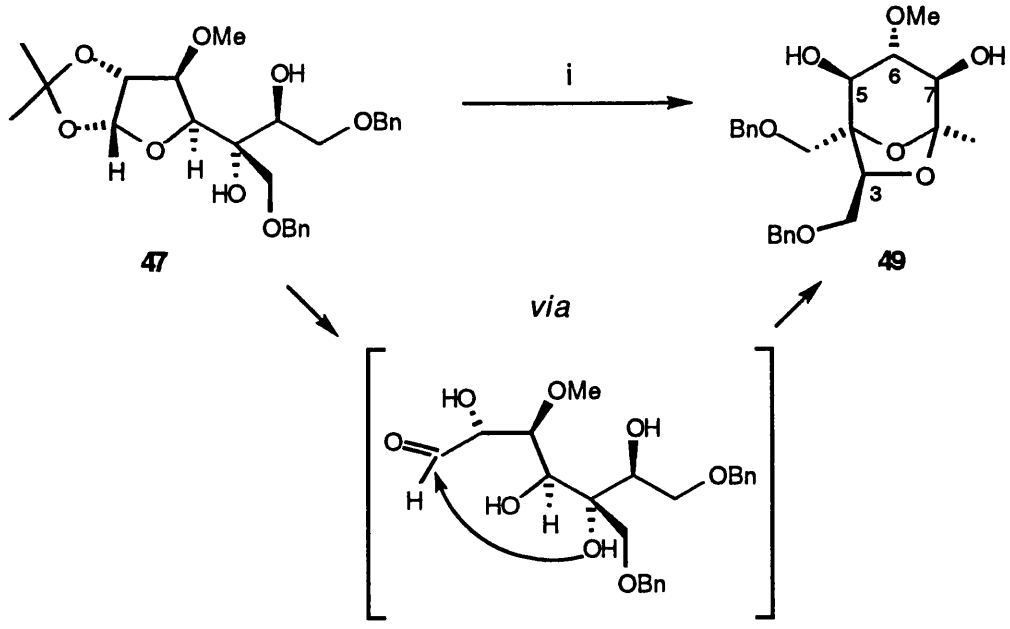
Reagents and conditions: i) OsO_4, NMO, acetone/water; ii) PTSA (cat.), $CHCl_3$, Δ, 100% **44+45**.

Interestingly, one of the diastereomers **46** did indeed now afford the desired 1,6-anhydrofuranose **48** (albeit being the opposite enantiomer with the incorrect stereochemistry at C3, C6 and C7 with respect to the natural product system) (Scheme 11). However, the other diastereomer **47** gave rise to the 1,6-anhydropyranose ketal isomer system **49** (Scheme 12).



Scheme 11

Reagents and conditions: i) PTSA (cat.), $CHCl_3$, Δ

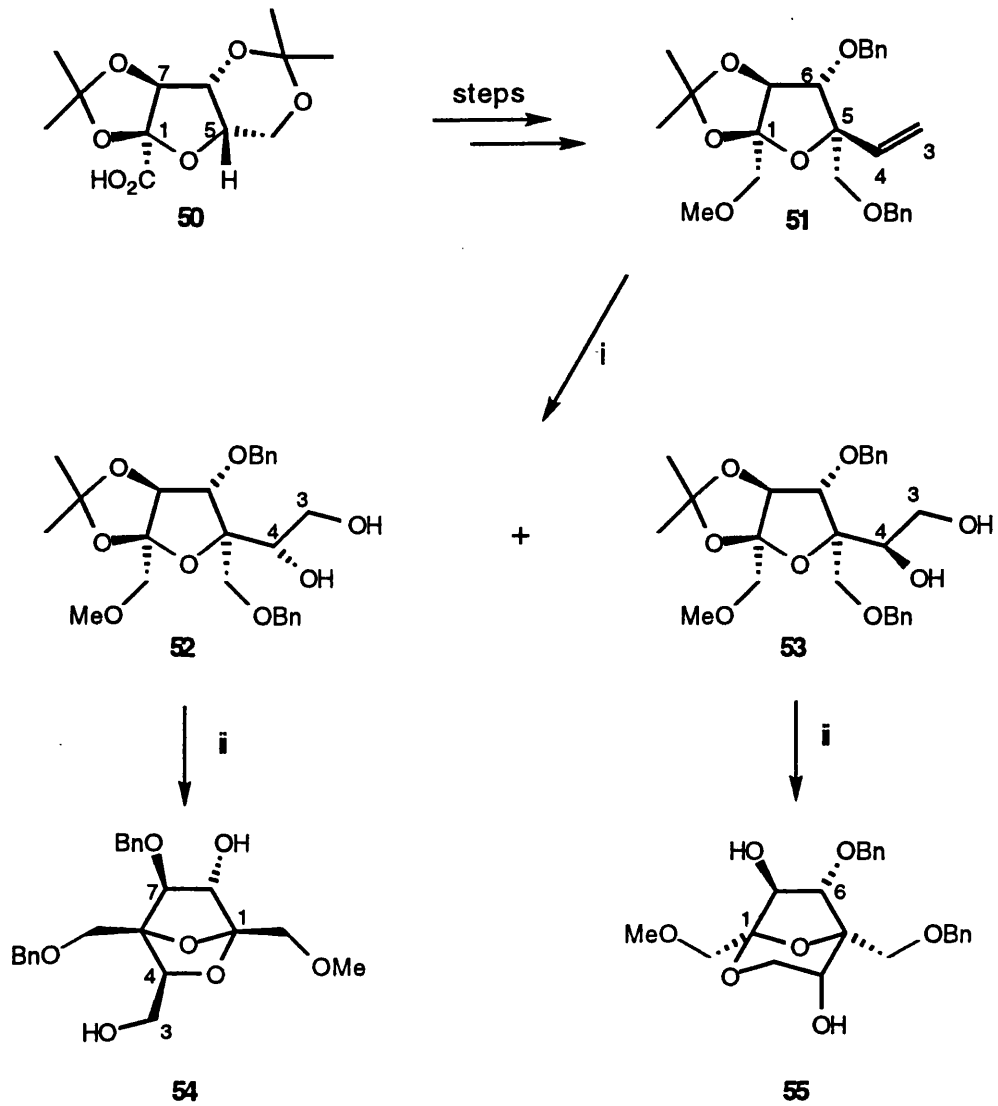


Scheme 12

Reagents and conditions: i) *p*-TsOH, $CHCl_3$, Δ

In a subsequent communication,[40] Gurjar again reported an apparent stereochemical dependence for anhydro-ring formation in another model system. The commercially available 2,3,4,6-di-*O*-isopropylidene-2-keto-L-gluconic acid **50** was converted into the olefinic furanose **51**. Catalytic osmylation afforded a 1:1.5 diastereomeric mixture of diols **52** and **53**. Acid-catalysed cyclisation of diol **52** afforded the 2,6-anhydro ring system **54**. However,

cyclisation of diol **53** gave the desired core **55** of the zaragozic acids (opposite enantiomer, lacking C3 substituent, but all other stereocentres correct) (Scheme 13).

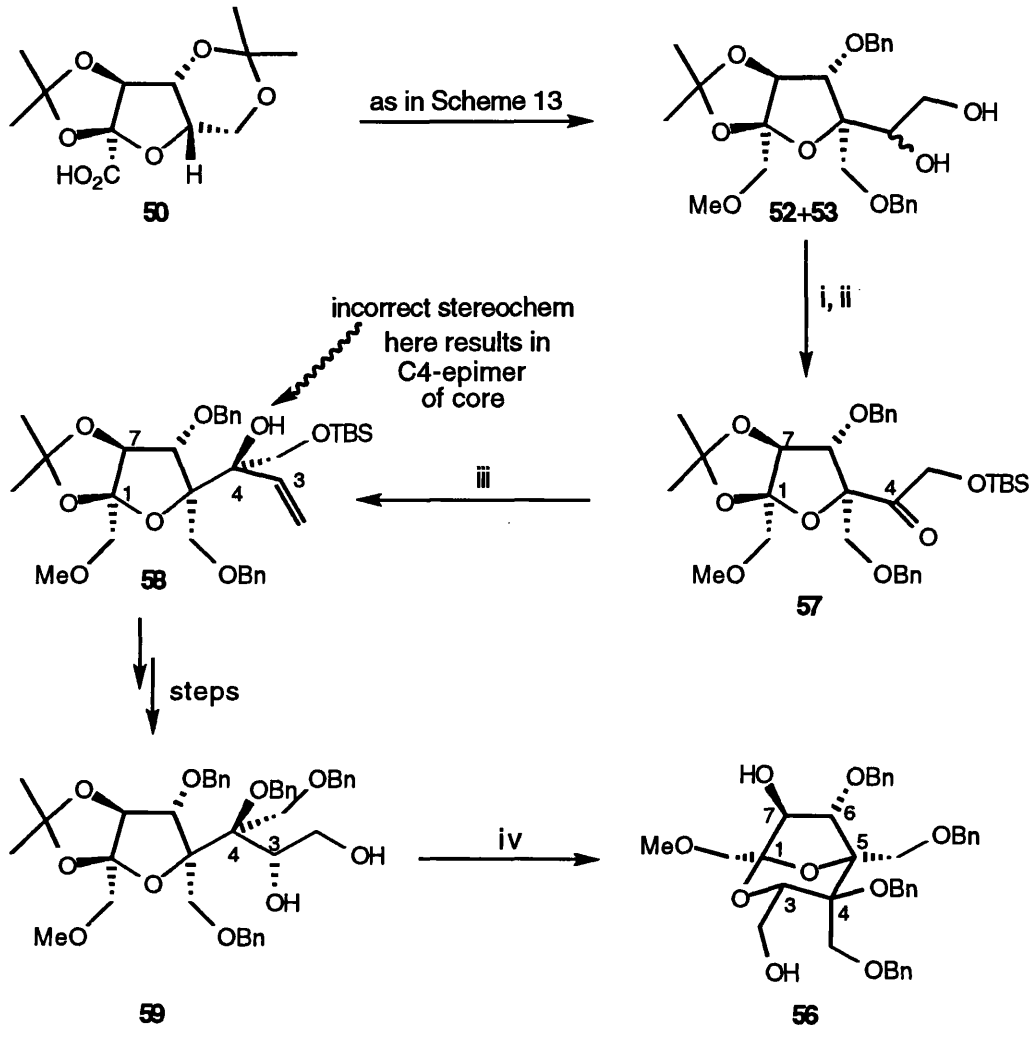


Scheme 13

Reagents and conditions: i) OsO_4, NMO, acetone/water; ii) PTSA (cat.), $CHCl_3$, Δ

A final communication from the Gurjar group[41] described modification of the previous route (Scheme 13) to include functionality at C3. The resultant core **56** (opposite enantiomer to the natural product) possesses the incorrect stereochemistry at C4, which arises from generation of the undesired diastereomer in the chelation controlled Grignard addition reaction to the 5-ulofuranose derivative **57** (Scheme 14). Thus, protection of the primary hydroxyls of the diastereomers **52** and **53** (prepared as in Scheme 13) followed by oxidation afforded the ketone **57**. Addition of vinylmagnesium bromide to **57** resulted in one diastereomerically pure

alcohol **58**, (incorrect configuration at C4). Subsequent steps gave the bicyclic precursor **59**, which on heating in $CHCl_3$ in the presence of tosic acid afforded the bicyclic core **56**.

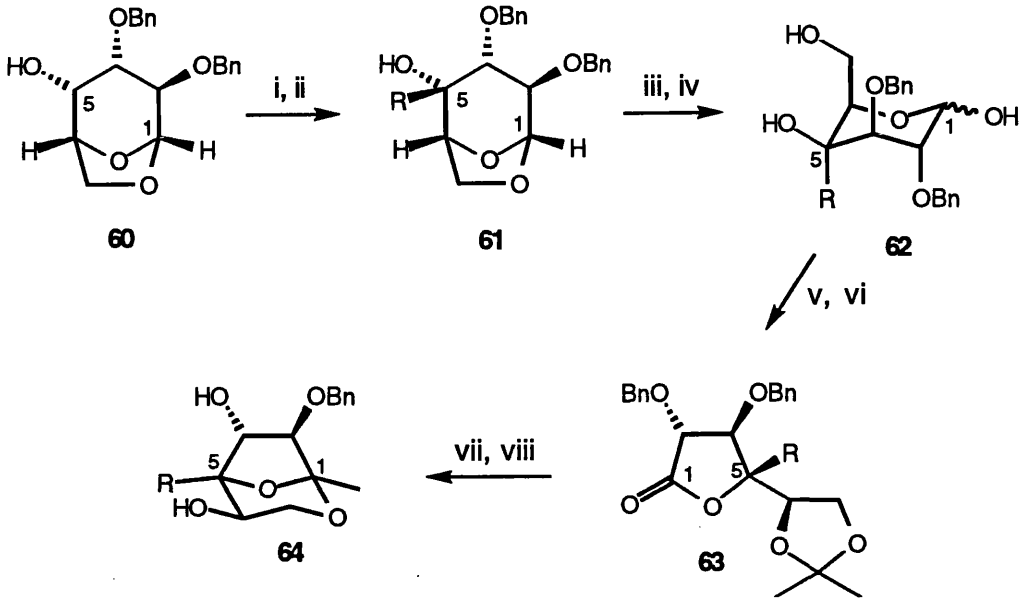


Scheme 14

Reagents and conditions: i) TBSCl, imidazole, CH_2Cl_2, RT, 3h; ii) DMSO, $(COCl)_2$, CH_2Cl_2, -78°C, Et_3N, 1.5h; iii) vinyl magnesium bromide, THF, 0°C to RT, 0.5h; iv) PTSA (cat.), $CHCl_3$, Δ.

Heathcock,[42] like Roberts, also utilised the 1,6-anhydropyranose moiety in his core synthesis in the form of the bis-benzyl protected derivative **60**. Oxidation followed by Grignard addition allowed for incorporation of functionality suitable to be turned into what would become the C5 carboxyl. Acetolysis of the anhydrosugar **61**, with concomitant acetylation followed by saponification gave an anomeric mixture of triols **62**. Selective ketalisation followed by oxidation with PDC afforded the corresponding γ-lactone **63**. Use of an organocerium reagent was necessary to incorporate the C1 functionality as use of the more

basic organolithium reagent led to elimination of the benzyloxy group at C3. Hydrolysis of the isopropylidene acetal afforded the 1,4-dialkyl-1,6-anhydrofuranose **64**, representing the model bicyclic core of the zaragozic acids (Scheme 15).



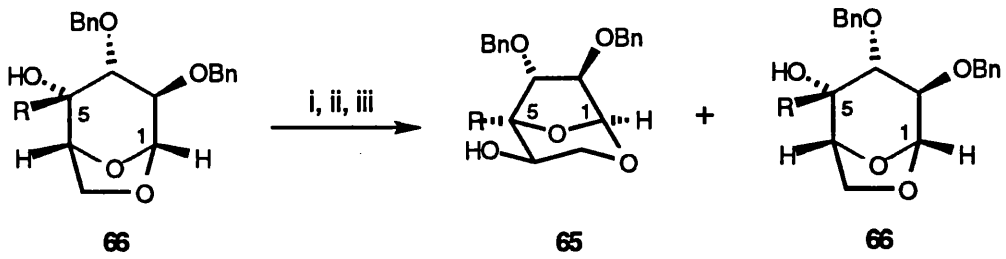
R = CH_2CH_2CHCH, Ph, $CH_2OTBDMS$

Scheme 15

Reagents and conditions: i) DMSO, TFAA, Et_3N, CH_2Cl_2, -78°C to RT, 87%; ii) RMgBr, THF, -78°C to RT, 82-92%; iii) TFA, Ac_2O, 65°C; iv) MeONa, MeOH; v) acetone, *p*-TsOH; vi) PDC, sieves, CH_2Cl_2, 41-76% from **61**; vii) $MeCeCl_2$, THF, -78°C; viii) 2N HCl, THF, reflux, 61-69% from **63**.

Heathcock then probed some of the factors influencing the preferential formation of the 1,6-anhydrofuranose derivatives in this model core study.

For the formation of 5-substituted 1,6-anhydrogalactofuranoses, it was found that as the electronegativity of the C5 substituent increases, the ratio of 1,6-anhydrofuranose **65** to 1,6-anhydropyranose **66** decreases (Scheme 16 and Table 3).



66 **65** **66**

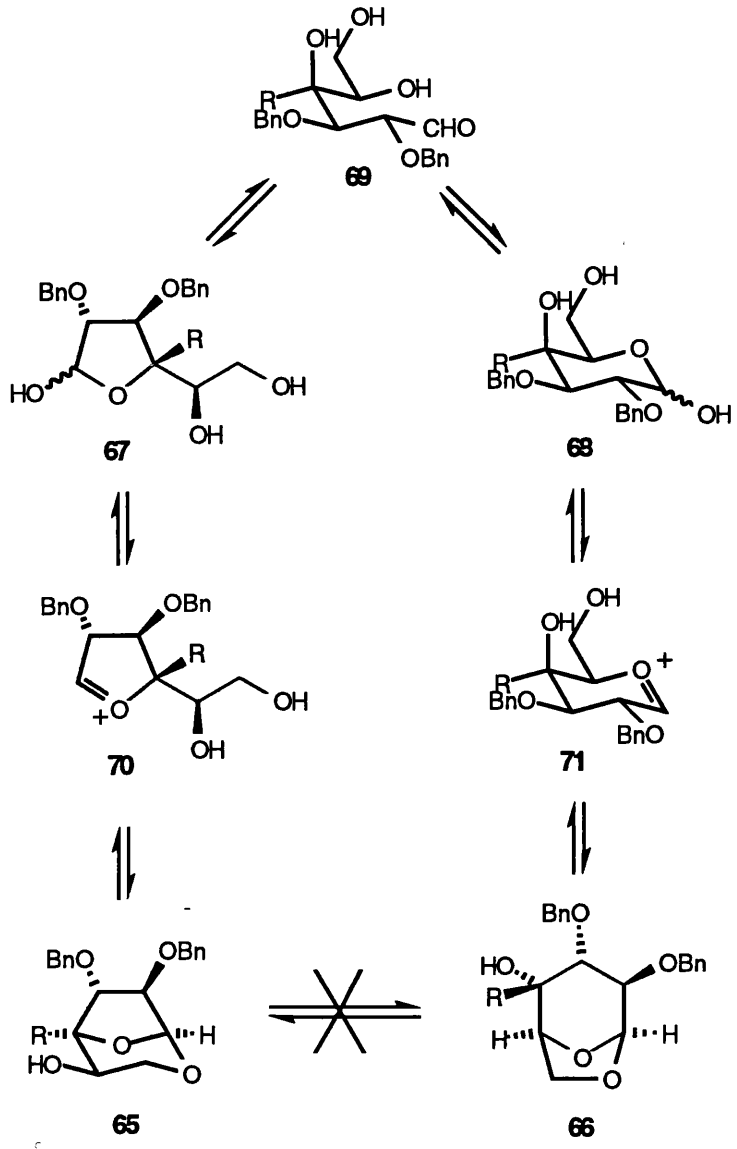
Scheme 16

Reagents and conditions: i) TFA, Ac_2O, 65°C; ii) MeONa, MeOH; iii) *p*-TsOH, C_6H_6, 48-79% from **66**.

Table 3: Dependence of **65**:**66** ratio on the nature of the C5 substituent

R	Substrate	Ratio **65**:**66**
Me	**66a**	>95:5
Et	**66b**	8:1
$CH_2CH{=}CH_2$	**66c**	4:1
Ph	**66d**	1:1
$CH_2OTBDPS$	**66e**	1:2
CO_2Et	**66f**	<5:95

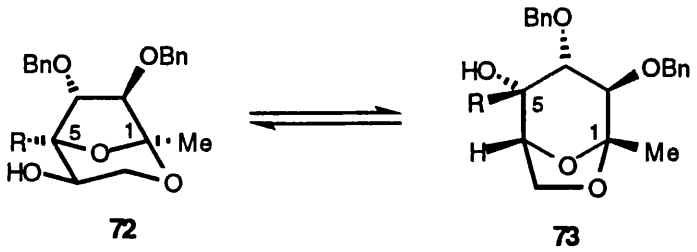
Control experiments showed that the product ratios are kinetic, and not thermodynamic. The trend was rationalised as follows. Under acidic conditions, the triols **67** and **68** should be under equilibrium *via* aldehyde **69**. Furanose **67** gives rise to the 1,6-anhydrofuranose **65** *via* the oxonium ion **70** and pyranose **68** generates the 1,6-anhydropyranose **66** *via* the oxonium ion **71**. Electronegative substituents R at C4 disfavour oxonium ion **70** more than oxonium ion **71** (Scheme 17) resulting in faster formation of **71**.



Scheme 17

However, when there was an additional subtituent present at C1, preferential formation of 1,4-dialkyl-1,6-anhydrofuranoses was observed. The desired 1,4-dialkyl-1,6-anhydrofuranoses are selectively generated kinetically (kinetic ratios for **72**:**73** 9:1 to >10:1), but now slowly equilibrate to the 1,4-dialkyl-1,6-anhydropyranoses. This time, however, the equilibrium ratio appears to reflect the steric size of the C5 substituent of the anhydropyranose, rather than the electronegativity, since increasing the size of the C5 substituent favours the wrong ketal isomer **73** (Table 4) .

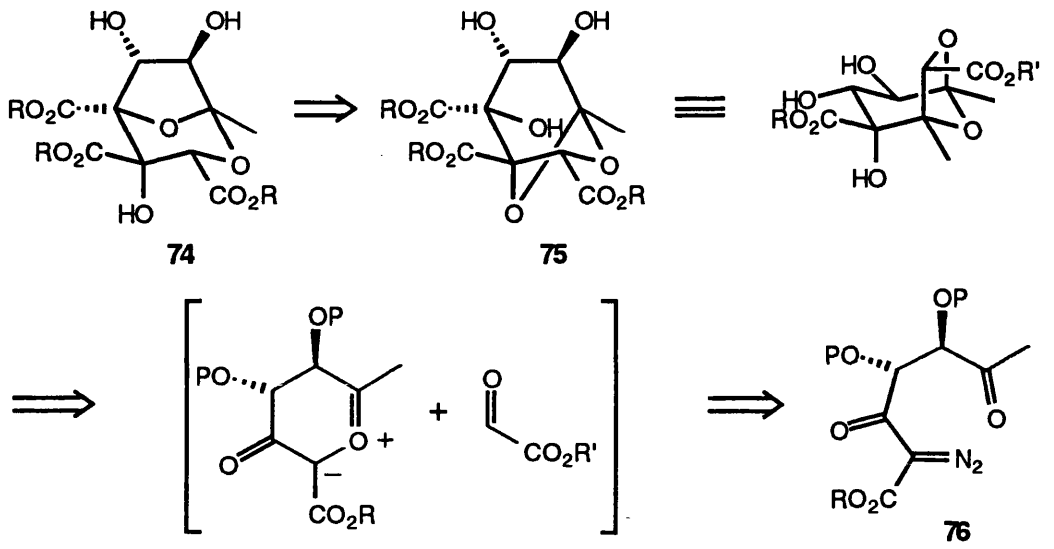
Table 4: Equilibrium ratios for cores with both C5 and C1 substituents.



72 73

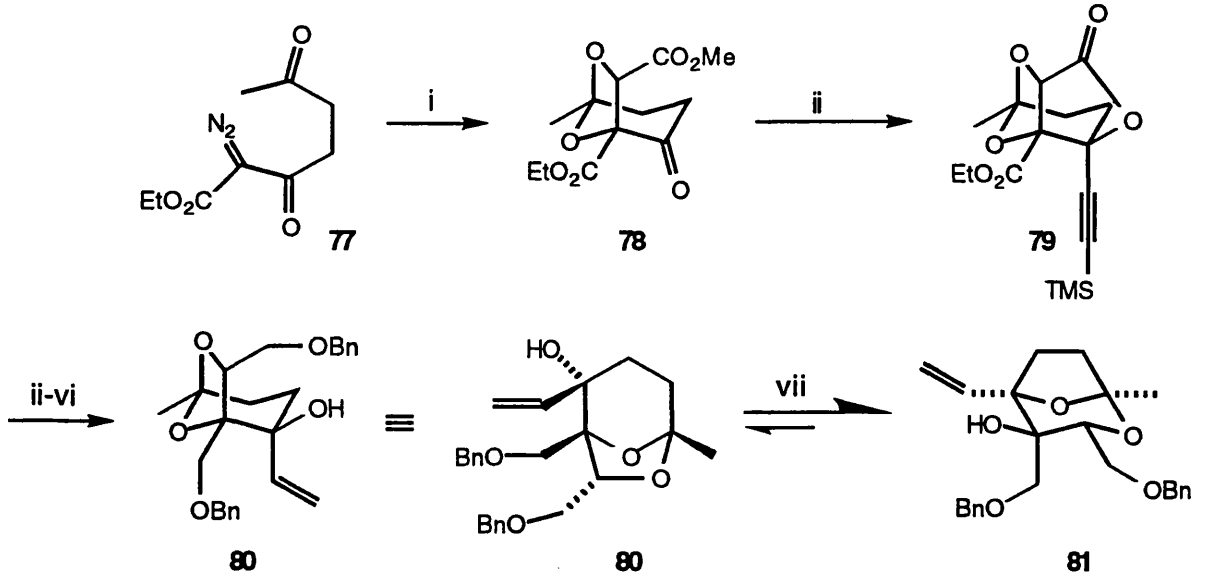
R	Substrate	Time	Ratio 72:73
$CH_2CH=CH_2$	**72a**	3h	2:1
$CH_2CH=CH_2$	**73a**	3.5h	2:1
Ph	**72b**	30 min	1:2
Ph	**73b**	90 min	1:2
$CH_2OTBDPS$	**72c**	75 min	1:1
$CH_2OTBDPS$	**73c**	1h	1:1

Another approach, utilising 1,3-dipolar cycloaddition chemistry followed by an acid-catalysed rearrangement of the 6,8-dioxabicyclo[3.2.1]octane to the desired 2,8-dioxabicyclo[3.2.1]octane ring system, has very recently been disclosed by the Hodgson group.[43] The retrosynthetic disconnections are shown below (Scheme 18). It was thought that the anhydrofuranose core **74** might be obtained *via* an acid-catalysed rearrangement of anhydropyranose **75**, which itself could be obtained via a 1,3-dipolar cycloaddition of the carbonyl ylide generated from the diazodiketoester **76**, followed by a ketone to hydroxy acid conversion.



Scheme 18

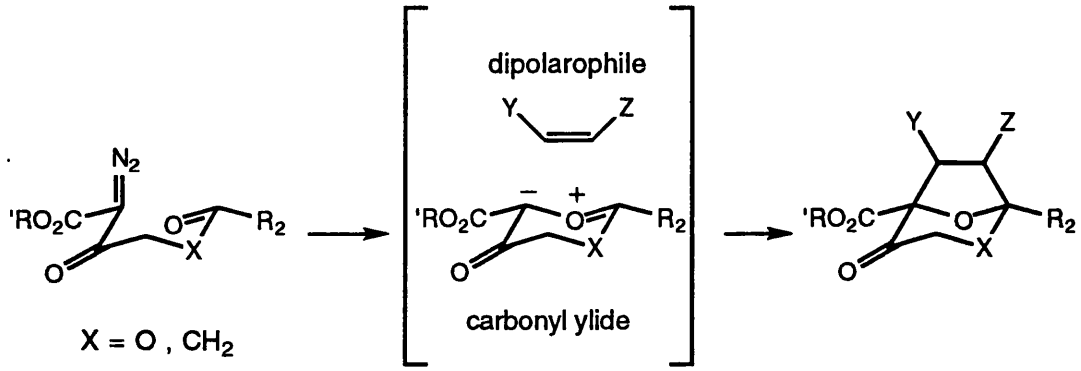
Treatment of the diazodiketo ester **77** with methyl glyoxylate in the presence of catalytic rhodium acetate afforded the *endo* cycloadduct **78** as a single isomer (Scheme 19). Addition of lithium trimethylsilyl acetylide, (to introduce a masked form of the remaining carboxylate unit), occurred exclusively under axial attack to give the lactone **79**. Treatment of the derived anhydropyranose **80** with acid led to the desired 2,8- rearrangement product **81** which existed in a 3:1 equilibrium mixture with the 6,8-dioxabicycle **80**.



Scheme 19

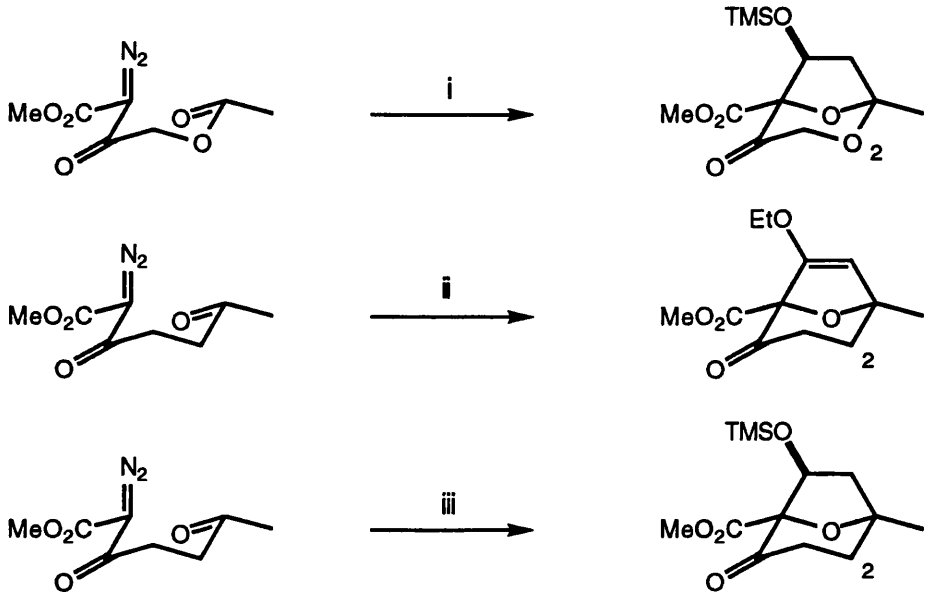
Reagents and conditions: i) methyl glyoxylate, cat. $Rh_2(OAc)_4$, toluene, reflux, 0.5h, 60%; ii) lithium trimethylsilylacetylide, THF, -78°C, 1h, 80%; iii) K_2CO_3, wet DMF, RT, 3h, 98%; iv) H_2 (1 atm.), Pd/C, RT, 2h, 100%; v) $LiAlH_4$, Et_2O, RT, 1d, 67%; vi) NaH, BnCl, cat. NaI, DME, 0°C to RT, 52%; vii) 2% HCl in MeOH, RT, 15 min.

Researchers at Merck had earlier reported a novel approach to the zaragozic acid core which also employed 1,3-dipolar cycloaddition chemistry between carbonyl ylides and various dipolarophiles.[44] This is the only model core synthesis not to rely upon a ketalisation process for forming the 2,8-dioxabicyclo[3.2.1]octane ring system. The bicyclic cores are obtained directly in one step from two acyclic precursors. The general strategy is outlined in Scheme 20.



Scheme 20

In all cases, slow addition of the diazo compound to the dipolarophile, in the presence of catalytic rhodium acetate, resulted in a single cyclisation product, of which a few examples are illustrated below (Scheme 21).

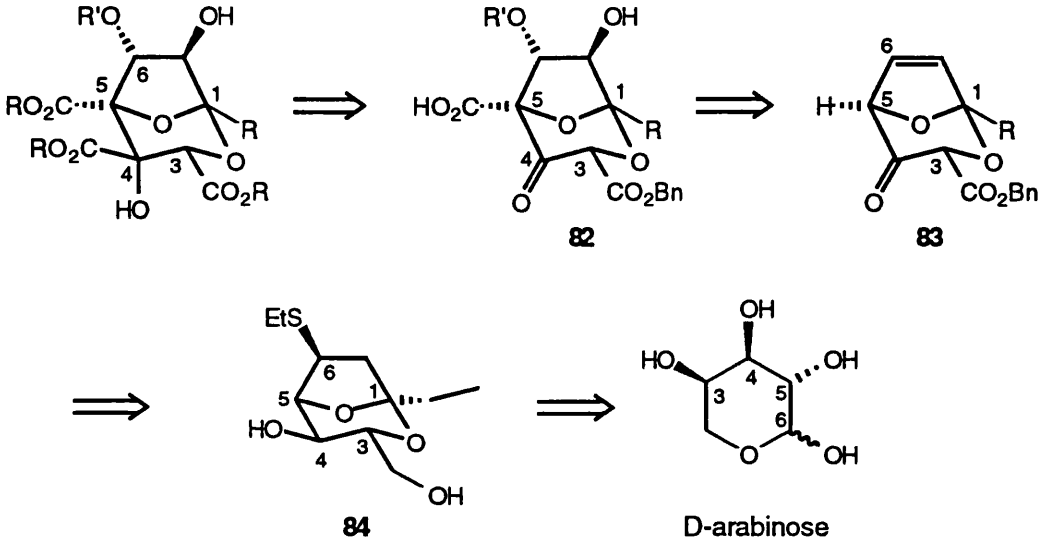


Scheme 21

Reagents and conditions: i) $Rh_2(OAc)_4$, $TMSOCH{=}CH_2$, PhH, 70°C, 16%; ii) $Rh_2(OAc)_4$, $EtOC{\equiv}CH$, PhH, 70°C, 72%; iii) $Rh_2(OAc)_4$, $TMSOCH{=}CH_2$, PhH, 70°C, 66%

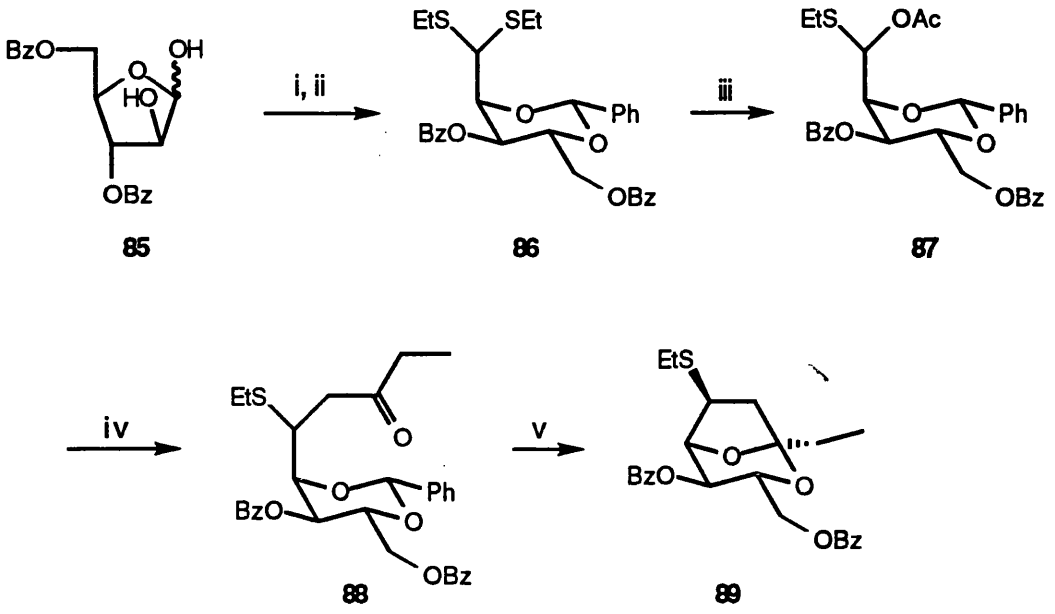
However, although reactions of the carbocyclic derivatives of the core (*i.e.* lacking the oxygen in the 2 position) generally proceeded smoothly and in good yields, the reactions containing the 2 position oxygen all proceeded in very low yields (9%-16%).

Finally, Kraus and co-workers have reported the synthesis of a model core system.[45] Their retrosynthesis involved introduction of the α-hydroxy acid subunit *via* the keto acid **82** which in turn would arise from carboxylation of the bridgehead position followed by oxidation of the alkene in the bicycle derivative **83**. Compound **83** itself was seen to arise from oxidation of a compound similar to diol **84** (Scheme 23).



Scheme 23

Conversion of hemiacetal **85**, (5 precedented steps from D-arabinose), into thioacetal **86**, followed by treatment with mercuric acetate in acetic acid produced the acetate **87** as a single diastereomer. Treatment of **87** with the enol silyl ether of 2-butanone afforded the ketone **88**, which cyclised to afford the bicyclic ketal **89** upon warming in methanol in the presence of catalytic *p*-TsOH (Scheme 24).



Scheme 24

Reagents and conditions: i) EtSH, HCl; ii) $PhCH(OMe)_2$, *p*-TsOH, 58% from **85**; iii) $Hg(OAc)_2$, AcOH, 92%; iv) 2-trimethylsilyloxybutene, $SnCl_4$, -78°C, 65%; v) *p*-TsOH (cat.), MeOH, 60°C, 69%.

This model core review highlights the fact that the factors affecting the formation of either the desired 1,6-anhydrofuranose, the undesired 1,5-anhydrofuranose or 1,6-anhydropyranose systems is not straightforward. The Gurjar group have shown there to be a stereochemical dependence as to which ketal isomer is formed under their reaction conditions. They report of no interconversion between their various ketal isomer systems. Hodgson (and Nicolaou, *vide infra*) on the other hand, reports of a thermodynamic ketal isomerisation, and indeed, it was the isomerisation of 1,6-anhydropyranose systems to 1,6-anhydrofuranoses that was the impetus for Heathcock's synthesis of the zaragozic acids. The factors influencing the formation of the correct ketal isomer are clearly complex, and will be discussed again later in Chapter 2.

All of these model core syntheses, impressive though they are, are clearly still a long way from the natural product itself. The following section reviews the total syntheses reported to date.

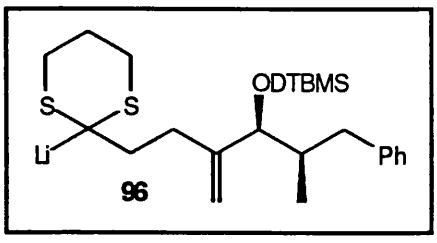
1.5.2 Published total syntheses of the zaragozic acids.

In 1994, Nicolaou reported the first total synthesis of this series of natural products; that of zaragozic acid A.[31]

Four of the six stereogenic centres of the core are constructed by dihydroxylations, the first of which employed the Sharpless asymmetric *cis*- dihydroxylation (AD) of the prochiral diene **90** to incorporate the initial chirality. Although the AD of the diene **90**, affording diol **91** in 83% ee, was low yielding, it is interesting to note that it is completely regioselective. Moreover, it has been the olefin conjugated to the ester that has been preferentially oxidised. This initially appears unlikely, since it is known that OsO_4 reacts slowly with electron poor olefins. However, to avoid allylic interactions, modelling has predicted that the ester group actually lies orthogonal to the plane, and hence overlap of the olefin π-system with the ester is no longer possible.

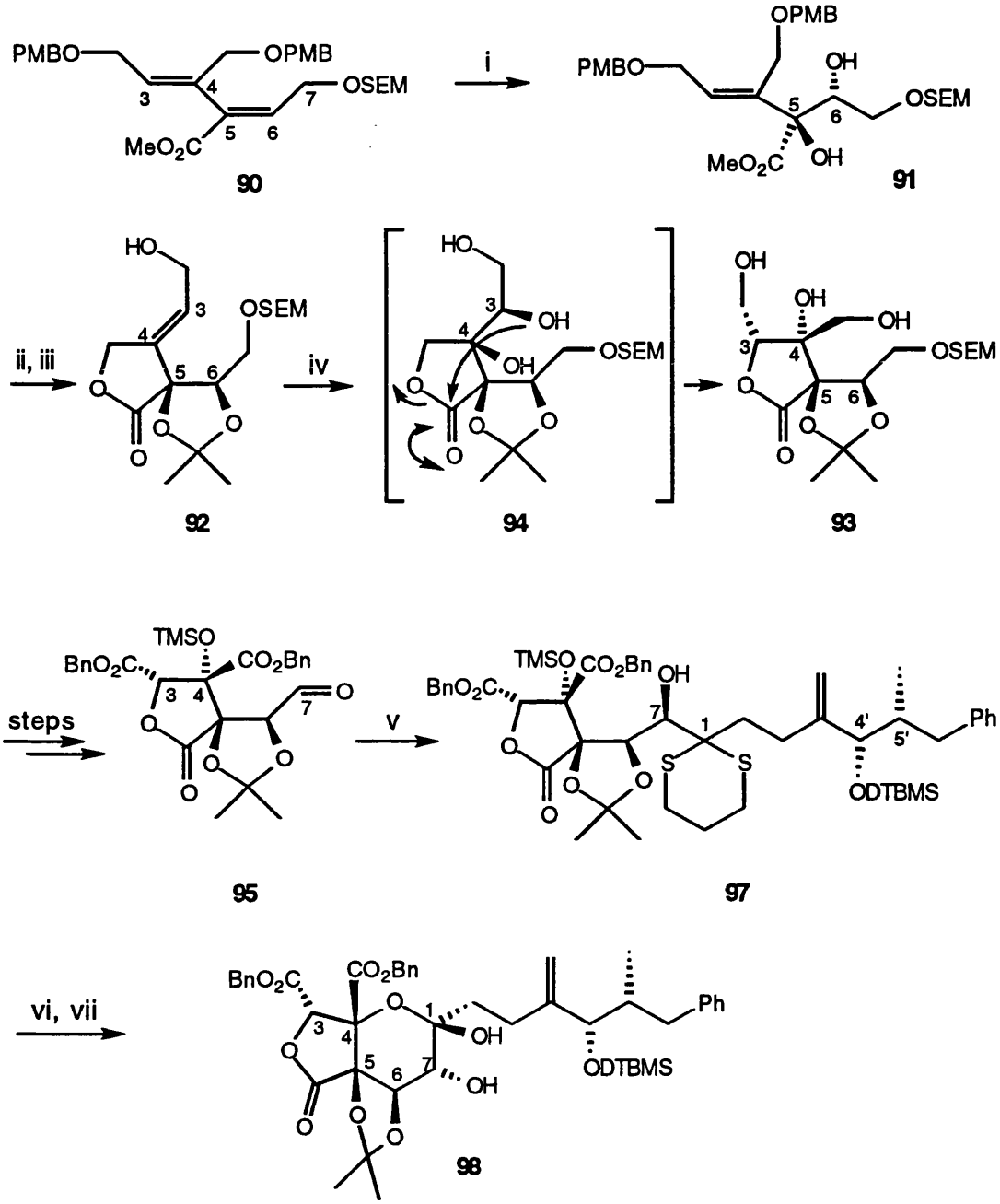
In the next key step, the second dihydroxylation of the lactone **92** afforded the triol **93** *via* the initially formed triol **94** followed by a spontaneous translactonisation. Subsequent manipulations involving stepwise oxidation of two of the hydroxymethyl groups to the carboxylic acid level furnished the key aldehyde **95**.

Installation of the C1 sidechain was achieved *via* addition of the lithiated dithiane **96** (serving as an acyl anion equivalent) to the aldehyde **95** to give the adduct **97**. However, this proceeded with poor diastereoselectivity giving approximately a 1:1 mixture of diastereomers, for which no conditions could be found to improve the selectivity. Hydrolytic cleavage of the desired diastereomer **97** then gave the lactol **98** (Scheme 25).



96

Nicolaou's acyl anion equivalent employing the rarely used di-*tert*-butylmethylsilyl protecting group.

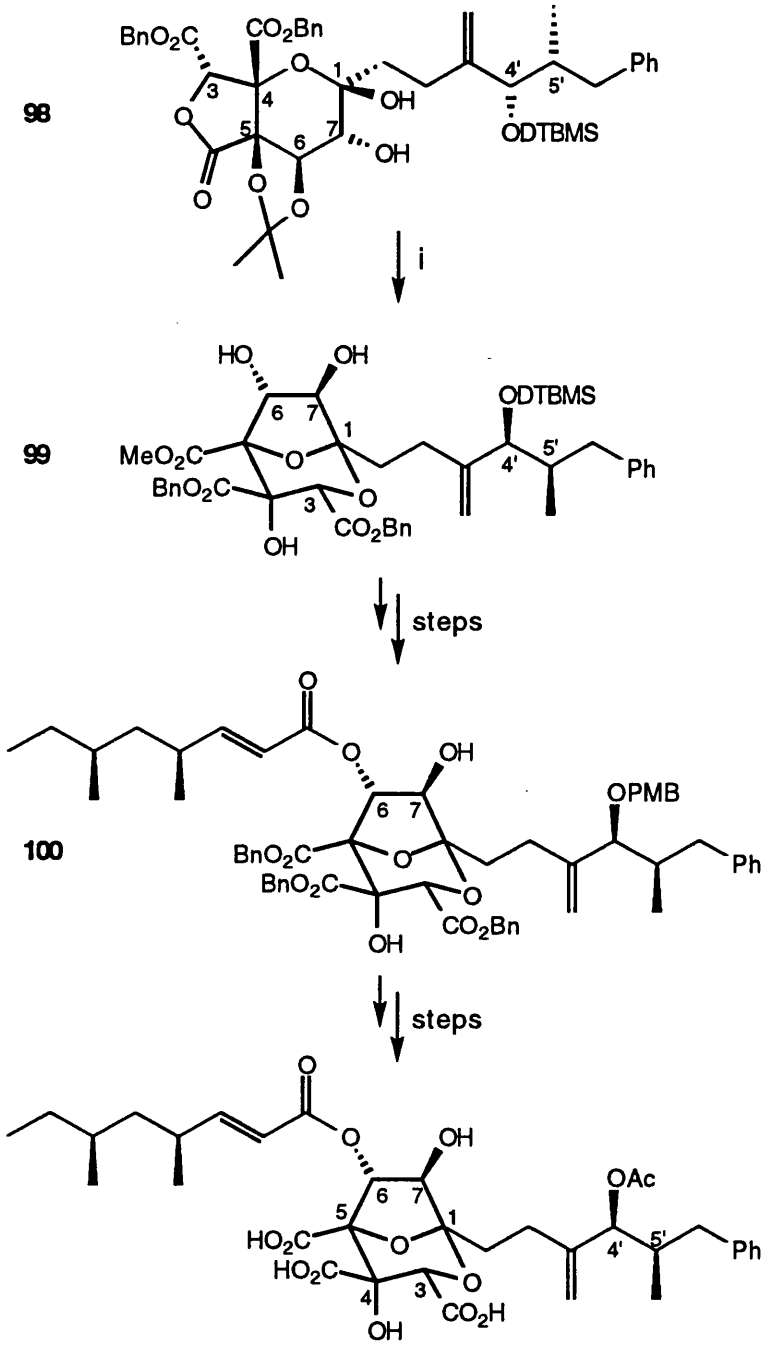


Scheme 25

Reagents and conditions: i) $(DHQD)_2$-PHAL, $K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, $^tBuOH/H_2O$, 0°C, 30%; ii) 2-methoxypropene, PPTS, 88%; iii) DDQ, $CHCl_3/H_2O$, 86%; iv) OsO_4, NMO, $^tBuOH/THF/H_2O$, 83%; v) **97**, THF, -78°C, 32%; vi) 2% HCl/MeOH, CH_2Cl_2, 99%; vii) $Hg(ClO_4)_2$, $CaCO_3$, THF/H_2O, 2.5h, 83%;

Subjection of the lactol **98** to 1.8% HCl-MeOH at reflux effected rearrangement to give the zaragozic acid A skeleton **99**. (Scheme 26). Incorporation of the C6 sidechain required selective esterification of the C6 hydroxyl in the presence of the C7 hydroxyl. However, esterification proceeded with a low 3:2 selectivity in favour of the desired C6 ester which after

subsequent steps gave **100**. A series of protecting group manipulations then afforded zaragozic acid A in an overall yield of 1%.



zaragozic acid A

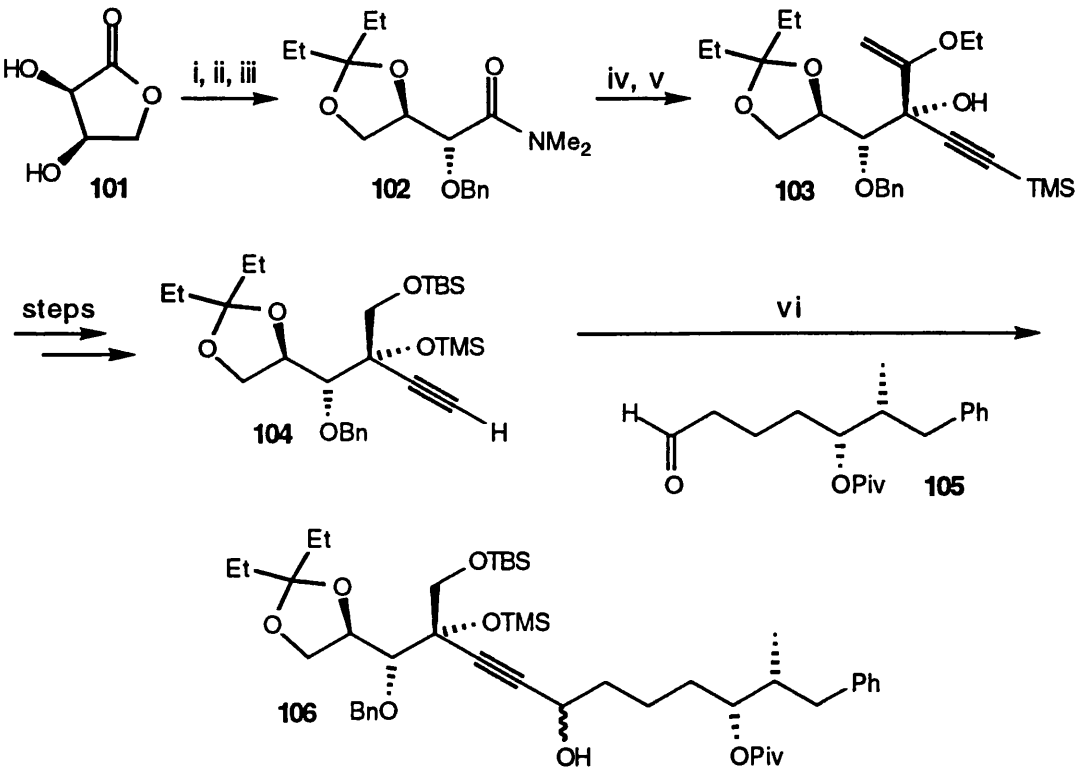
Scheme 26

Reagents and conditions: i) 2% HCl/MeOH, 78°C, 21h, 45%.

At the same time as the disclosure of this work by the Nicolaou group, Carreira published the total synthesis of zaragozic acid C.[32] Unlike the Nicolaou synthesis, Carreira

assembled the core such that the C1 sidechain is incorporated at an early stage in the synthesis, and has the tri-carboxylic acid unit at the hydroxymethyl oxidation level. This approach allows for the rapid construction of the bicyclic core.

The synthesis began with the condensation of D-erthronic γ-lactone **101** with dimethylamine which after protection afforded the amide **102**. Addition of 1-ethoxyvinyllithium to **102** yielded an intermediate ketone which underwent a chelate stereocontrolled addition with trimethylsilylethynyl magnesium bromide to provide the alcohol **103** as a 20:1 diastereomeric mixture. Subsequent manipulations led to the alkyne **104** which was coupled to the C1 sidechain **105** to afford a mixture of the propargylic alcohols **106** (Scheme 27).

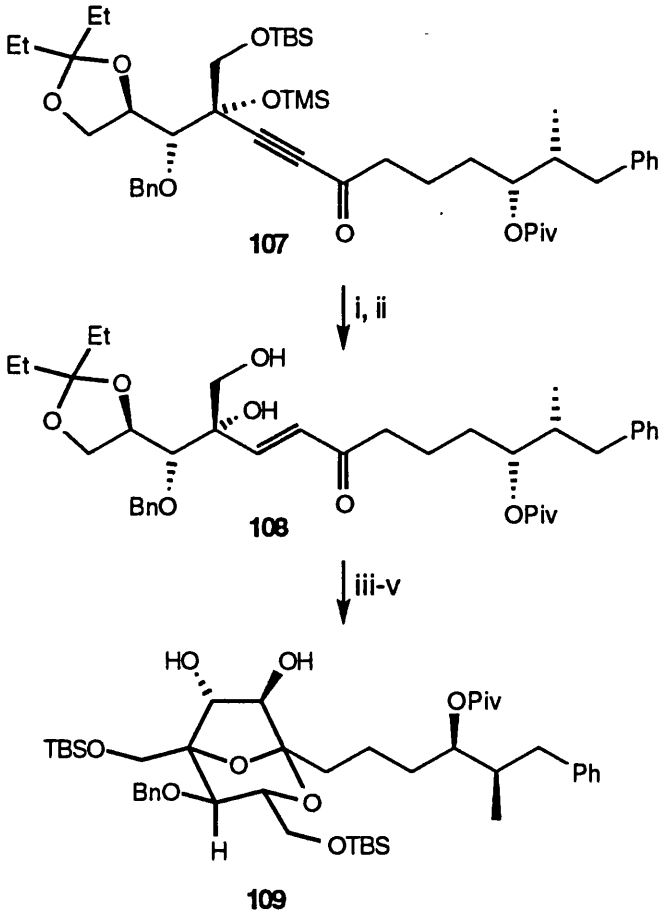


Scheme 27

Reagents and conditions: i) Me_2NH, MeOH, 0°C, 97%; ii) $(MeO)_2CEt$, *p*-TsOH, 90%; iii) NaH, BnBr, THF, 96%; iv) (ethoxyvinyl)lithium, THF, -78°C, v) TMSC≡CMgBr, THF, -78°C, 84%; vi) ^nBuLi, THF, -45°C then **105**, LiBr, THF, 93%.

Dess-Martin oxidation of **106** afforded the α,β-unsaturated ynone **107**. Stereoselective reduction of the ynone **107** to the corresponding *trans*-enone was accomplished using chromium (II) acetate monohydrate dimer, and subsequent removal of the silyl ethers gave

enone **108** (Scheme 28). It is interesting to note that dihydroxylation of enone **108** in the presence of *either* Sharpless ligand $(DHQ)_2$-PHAL or $(DHQD)_2$-PHAL afforded the same 1.7:1 diastereomeric mixture of tetraols in favour of the desired product. The two diastereomers isolated could not be separated at this stage. Cyclisation of the mixture with 0.5% HCl-MeOH afforded the corresponding 2,8-dioxabicyclo[3.2.1]octane cores, which were separated following selective protection of both primary hydroxyls as TBS ethers to afford the bicyclic core **109**.

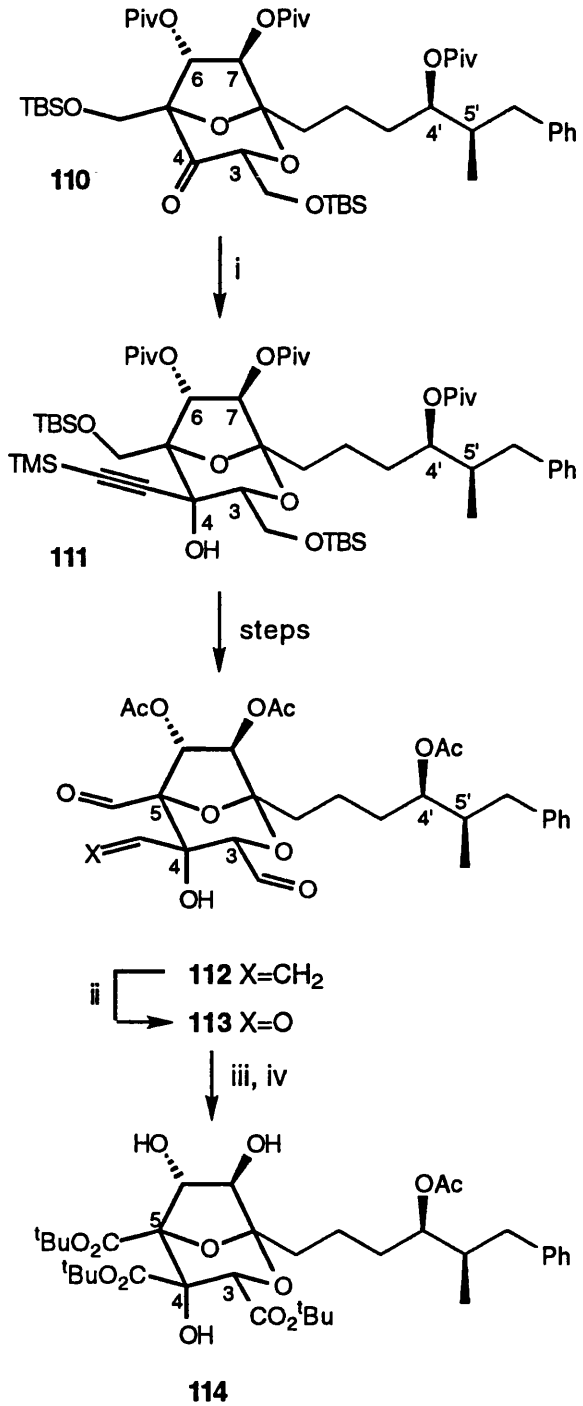


Scheme 28

Reagents and conditions: i) $[Cr(OAc)_2 \cdot H_2O]_2$, THF/H_2O, 60%; ii) ^nBu4NF, THF, 93%; iii) OsO_4, $(DHQD)_2$-PHAL or $(DHQ)_2$-PHAL, NMO, $acetone/H_2O$; iv) 0.5% HCl/MeOH, RT, 2h; v) TBSCl, Et_3N, DMAP, CH_2Cl_2, 26% from **108**.

The next key step was the introduction of a masked form of the C4 carboxylate. This was achieved by addition of lithium trimethylsilyl acetylide in the presence of trimethylamine to the C4 ketone **110** to give the alkyne **111** as a 6:1 diastereomeric mixture. Oxidation of the C3, C4 and C5 positions to the tri-carboxylic acids was achieved *via* simultaneous oxidation of

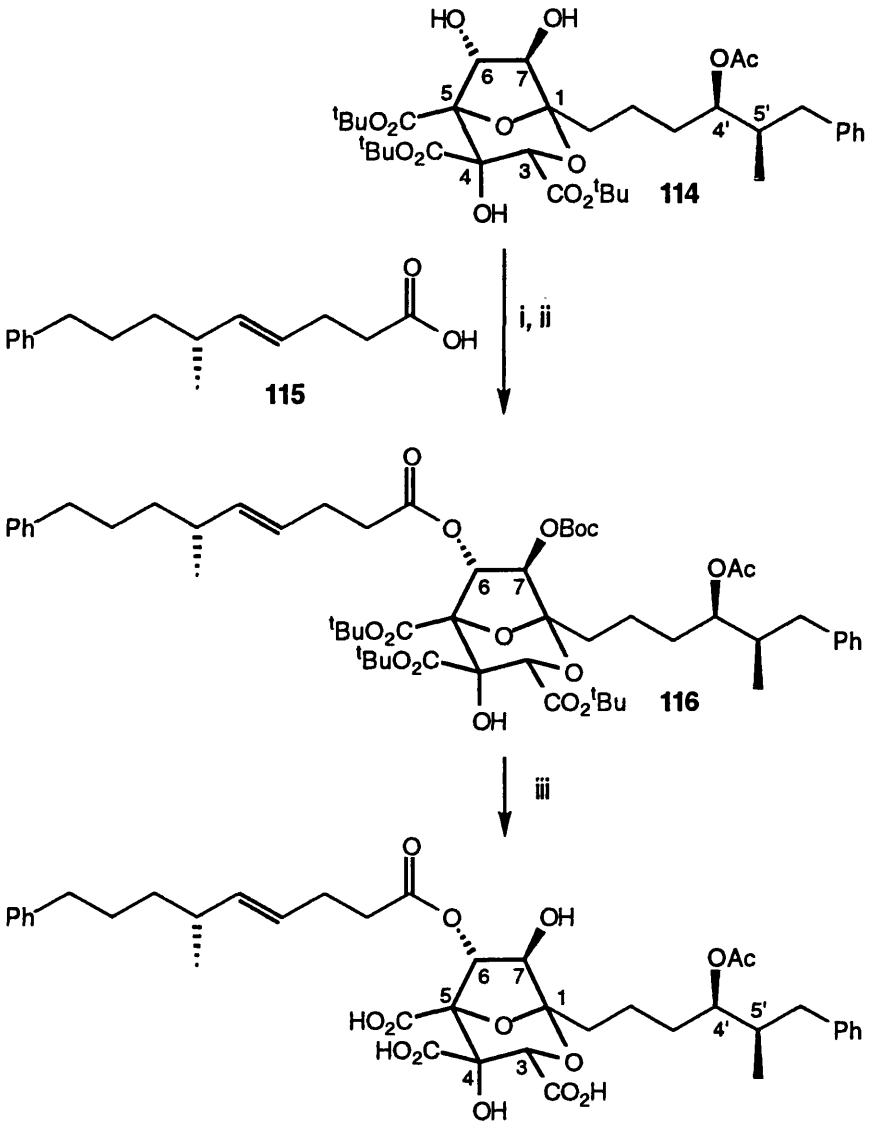
C3 and C5 hydroxymethyl functionalities to the corresponding di-aldehyde **112.** Ozonolysis of the double bond in **112** gave the tri-aldehyde **113** which then underwent a triple Pinnick oxidation to give the corresponding tri-carboxylic acid **114** (Scheme 29).



Scheme 29

Reagents and conditions: i) $TMSC{\equiv}CLi$, Et_2O/Me_3N (1:1), -78°C to -20°C, ii) O_3, CH_2Cl_2/MeOH, -78°C, iii) $NaClO_2$, NaH_2PO_4, β-isoamylene, THF/H_2O; iv) *N,N'*-diisopropyl-*O-tert*-butylisourea, CH_2Cl_2, 72% from **112.**

Selective Boc protection of the C7 alcohol of triol **114** using 4-(1-pyrrolidinyl)pyridine as the catalytic base allowed for the installation of the C6 sidechain **115** to give **116**, complete deprotection of which was effected with TFA to afford zaragozic acid C (Scheme 30).



zaragozic acid C

Scheme 30

Reagents and conditions: i) $(Boc)_2O$, 4-pyrrolidinopyridine, CH_2Cl_2, 82%; ii) **115**, DCC, DMAP, CH_2Cl_2, 78%; iii) TFA, CH_2Cl_2, 100%.

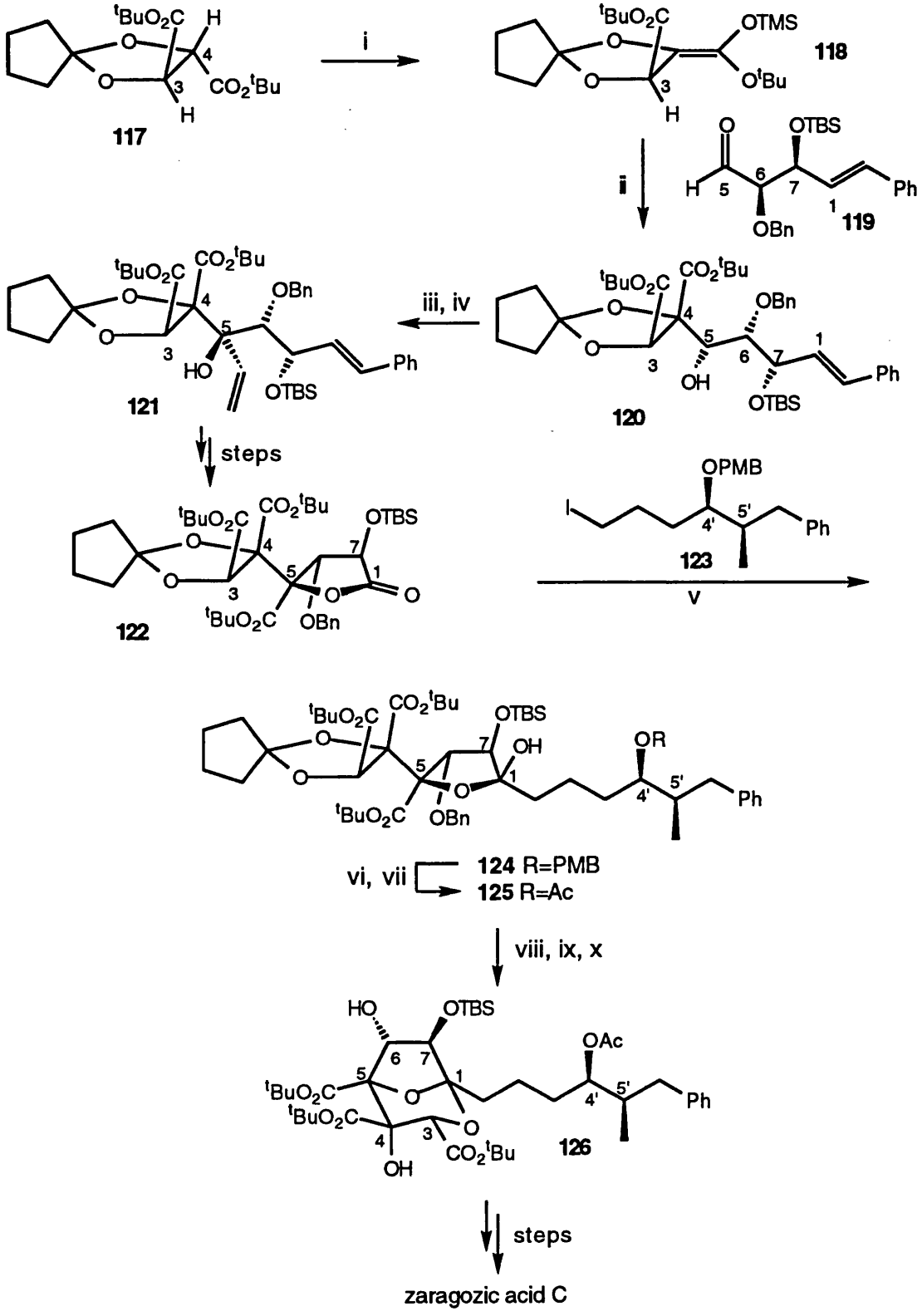
The third total synthesis to be discussed is that of zaragozic acid C by the Evans group.[33] Evans identified a tartaric acid unit in the C3-C4 portion of the bicyclic core of the zaragozic acids. Thus the synthesis commenced with the tartaric acid derivative **117**.

Enolisation of the ketal **117** with *in situ* silylation afforded the silyl ketene acetal **118** which underwent a stereoselective Lewis acid-catalysed aldol addition with aldehyde **119** to give adduct **120** as a single isomer (Scheme 31). Oxidation of **120** to the ketone followed by a chelation controlled addition of vinylmagnesium bromide introduced the latent C5 carboxyl moiety in the form of a vinyl substituent to give **121**. Selective dihydroxylation of the phenyl-substituted olefin of **121**, followed by diol cleavage, lactonisation and subsequent oxidation level adjustments afforded the lactone **122**. Addition of the C1 sidechain **123** to **122** led to the lactol **124**. Oxidative cleavage of the C4' *p*-methoxybenzyl ether followed by acetylation gave the lactol **125**. Submitting lactol **125** to the ketalisation / hydrolysis step afforded the tris-acid bicyclic core. Re-esterification and hydrogenolysis of the C6 benzyloxy substituent afforded the diol **126** which was coupled to the C6 sidechain **115**. Deprotection of the C7 silyl ether and C3, C4, C5 esters provided zaragozic acid C.

The final total synthesis is that of zaragozic acid A by the Heathcock group.[34] To date, this has only been reported in conference proceedings, and has yet to appear in the literature, and hence it will not be discussed here.

Since the first reports of the zaragozic acid/squalestatin family, over 100 papers have appeared in the scientific literature ranging from their isolation and characterisation, to their complete total syntheses. Much progress has been made in the synthetic area, and new problems and challenges have been met during that time, with the boundaries of synthetic chemistry being advanced ever forward. It is interesting to note that all three total syntheses not to mention numerous model core syntheses presented in this Chapter have employed the dihydroxylation reaction, highlighting the power and scope of this synthetic procedure.

This section has given an overview of the total syntheses to date, and in the following section, our route to the zaragozic acids will be described.



Scheme 31

Reagents and conditions: i) LiHMDS, TMSCl, THF, -78°C to 0°C, 97%; ii) (^{i}PrO)$TiCl_3$, CH_2Cl_2, 2h at -78°C then 2.5h at -40°C, 76%; iii) Dess-Martin oxidation, 94%; iv) CH_2=CHMgBr, CH_2Cl_2/THF, -78°C, 10h, 76%; v) 1.7 equiv of **123**, 3.4 equiv of *tert*-butyllithium, 1:1 hexane/ether, -78°C, 5 min, then **122**, -78°C, 15 min, 73%, vi) DDQ, CH_2Cl_2/H_2O, 1h, vii) Ac_2O, DMAP, pyridine, PhH, 1h, 90% from **124**; viii) 20:10:1 CH_2Cl_2/TFA/H_2O, RT, 14h, ix) 7 equiv *N,N'*-diisopropyl-*O-tert*-butylisourea, CH_2Cl_2, 52% from **125**; x) H_2, 750 psi, 10% Pd/C, AcOH, MeOH, 20h, 96%.

1.6 Retrosynthetic Analysis of the Zaragozic acids

Retrosynthetically, it becomes immediately apparent that the zaragozic acids can be broken down into three distinct fragments: the C6-acyl sidechain, the C1 alkyl sidechain, and of course the bicyclic core itself. Any synthetic approach not only has to contend with the stereoselective introduction of the numerous stereogenic centres, but also has to take into account the high density of oxygen-containing functional groups.

Our convergent approach to the zaragozic acids envisaged late attachment of the C6-acyloxy sidechain, and this plan required a suitably protected 2,8-dioxabicyclo[3.2.1]octane core. We desired a synthesis that would in principle be flexible enough to allow for the synthesis of any of the zaragozic acids. A strategy of this type would no doubt require a common intermediate. Also, given that the Merck and Glaxo SAR studies highlighted the importance of the C5 carboxylate,[27, 28] we planned to include the potential to differentiate the C5 acid in our synthesis, should it be required.

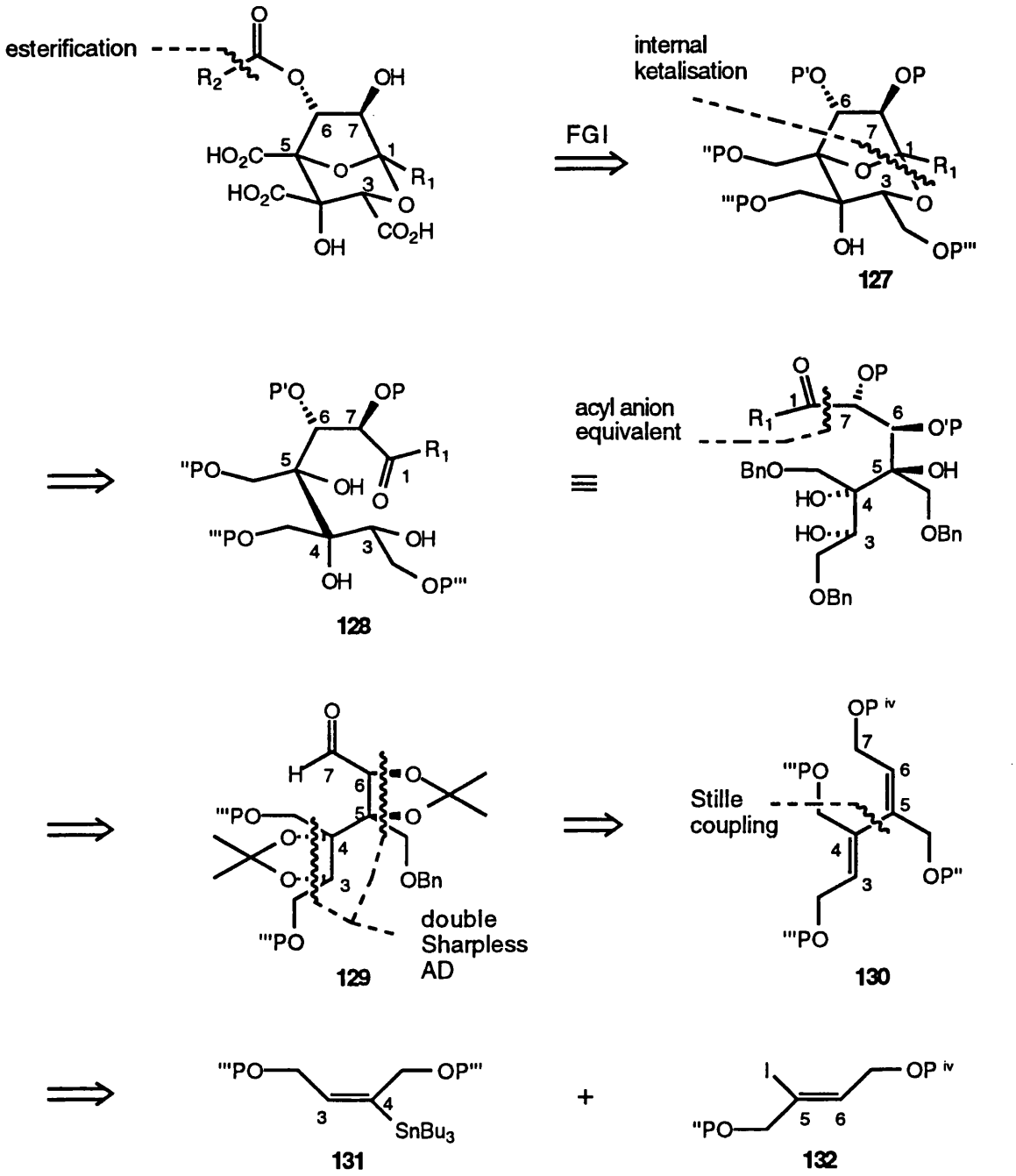
A route to the core could be envisaged *via* epoxide cyclisation routes, the idea of which was stimulated by Glaxo's biosynthetic proposal (see Scheme 4, Section 1.3). This would require stereoselective oxidation of a diene. However, this is difficult to achieve as it requires reliable asymmetric epoxidation of isolated alkenes and also control in ring size of epoxide opening. Therefore, it was thought to be easier to examine asymmetric osmylation reactions of dienes.

Our retrosynthetic analysis of the zaragozic acids is shown in Scheme 32. Since it is well known that dihydroxylation of alkenes is faster with electron rich double bonds, the carboxylic acids have been reduced to the alcohol oxidation level. Disconnection of the C6-acyloxy sidechain gave **127**, envisaging selective re-acylation at C6. It can be seen that the acyclic precursor **128** is just the open chain dihydroxy ketone form of **127**. At the start of our work there was no precedent for the formation of the desired bicyclic anhydrofuranose ring system. We therefore hoped that acid-catalysed internal ketalisation of the acyclic precursor **128** would on thermodynamic grounds lead to the formation of the desired bicyclic ketal core **127** rather than the 1,6-anhydropyranose or 1,5-anhydrofuranose structural isomers. The acyclic precursor **128** could be obtained by addition of an acyl anion equivalent (serving to

incorporate the C1 sidechain) to aldehyde **129**. It would be necessary to carry out this addition under chelation control in order to incorporate the C7-hydroxyl with the correct stereochemistry. This key disconnection provides an excellent opportunity for late stage divergency and, as was our plan, allows for access to any of the zaragozic acids by having the appropiately functionalised acyl anion equivalent. Therefore, aldehyde **129** would serve as our common intermediate.

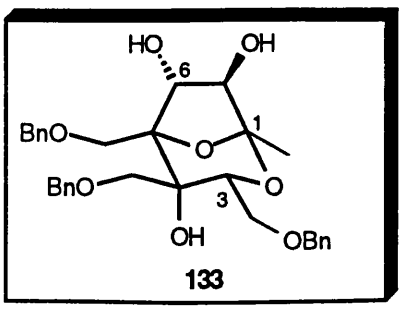
Removal of the two adjacent 1,2-diol functionalities of **129** leads to the prochiral 1,3-diene **130**. In the synthetic direction, it was planned to carry out a double Sharpless asymmetric *cis*-dihydroxylation[46] of the diene **130** to simultaneously control the stereochemistry of the four contiguous stereocentres at C3, C4, C5 and C6. The key point to note here is that both double bonds of diene **130** require the same chiral ligand for correct facial selectivity in the dihydroxylations. Since there would be no mismatch with the ligand, we aimed to incorporate all four contiguous stereocentres at once in a one-pot double Sharpless AD of diene **130**. Synthesis of the 1,3-diene **130** could be realised by way of a palladium mediated cross-coupling between the stereodefined vinyl stannane **131** and the vinyl iodide **132**, a transformation commonly known as a Stille-coupling.[47] It is worth mentioning that both the C3-C4 and C5-C6 relative stereochemical relationships in **129** stem directly from pre-defining the stereochemistry of the vinyl coupling partners **131** and **132** respectively.

As with many total syntheses, model studies are frequently performed on simplified systems prior to focusing attention towards the target molecule itself. Indeed, our initial target would be compound **133** where we have replaced the C1 sidechain with a methyl substituent, removed the C6 sidechain, and reduced all three carboxylic acids to the protected hydroxymethyl oxidation level.



Scheme 32: Our retrosynthetic analysis of the zaragozic acids

This thesis describes the successful synthesis of the bicyclic core **133** and subsequent attempts to elaborate the synthesis *en route* to a total synthesis of zaragozic acid D.



133

CHAPTER 2

Results and Discussion

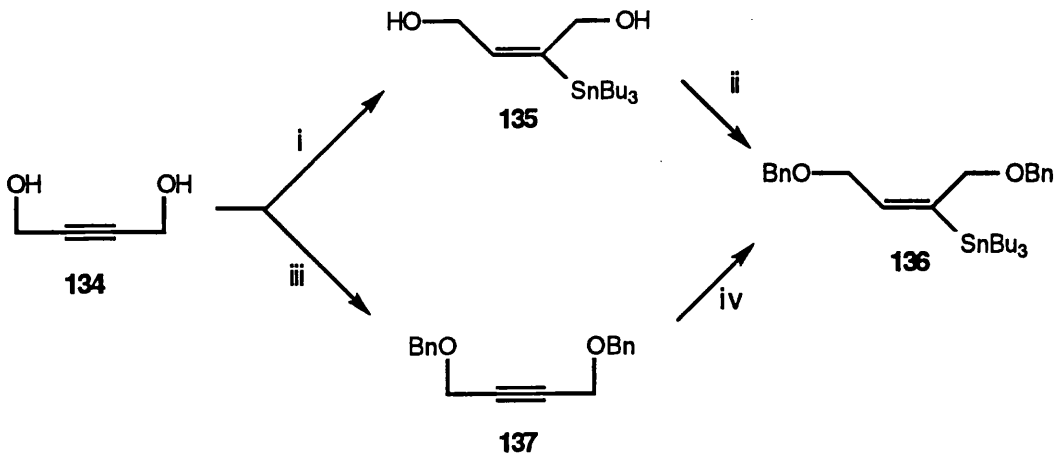
As outlined in our retrosynthesis, our prochiral 1,3-diene would be constructed using Stille coupling methodology between a stereodefined vinyl stannane and vinyl iodide. Therefore, these two alkenes became our initial synthetic targets.

2.1 Synthesis of the vinyl stannane

We required our vinyl stannane to have the two carbon substituents in a *syn* arrangement. A very efficient procedure for the stereospecific *syn* hydrostannylation of alkynes had been reported by Guibe and co-workers.[48] In the presence of catalytic amounts of dichlorobis(triphenylphosphine)palladium or a π-allyl molybdenum complex, tributyltin hydride was found to undergo a stereospecific *cis*-addition to a variety of alkynes to give the corresponding vinyl stannanes in good to excellent yields.

Following this literature procedure, treatment of but-2-yne-1, 4-diol **134** with $^{n}Bu_3SnH$ under palladium catalysis afforded exclusively the *cis*-hydrostannylation product **135** in 90% yield (Scheme 33).

Benzylation of **135** was first attempted using BnBr / NaH in DMF but these proved not to be the conditions of choice since an unidentified, inseparable side-product was formed as the reaction progressed. Benzylation using benzyltrichloroacetimidate also proved ineffective due to poor solubility of **135** in the 2:1 cyclohexane/CH_2Cl_2 solvent system, and by-products resulted when a more polar solvent was employed. However, it was found that addition of a catalytic amount of Bu_4NI to the NaH / BnBr / DMF system dramatically increased the rate of reaction. This minimised formation of the unwanted side-product and hence gave pure **136** in 71% yield. However, it was later found to be more effective to initially protect the diol **134** as the bis-benzyl ether **137** and then carry out the cis-hydrostannylation, which afforded the desired vinyl stannane **136** in 94% overall yield over two steps.[49]



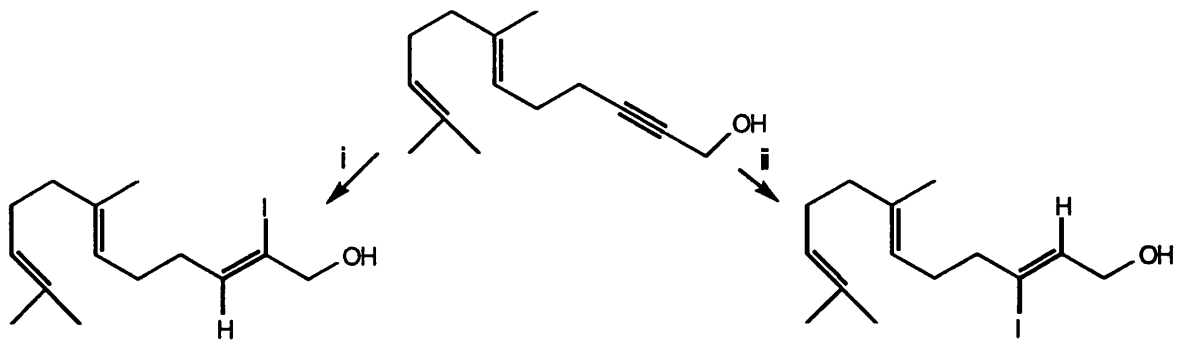
Scheme 33

Reagents and conditions: i) $^{n}Bu_3SnH$, 2 mol% $Pd(PPh_3)_2Cl_2$, THF, RT, 10 min, 90%; ii) NaH, BnBr, $^{n}Bu_4NI$ (cat.), DMF, 2.5h, 71%; iii) BnBr, $^{n}Bu_4NI$ (cat.), DMF, 95%; iv) $^{n}Bu_3SnH$, 2 mol% $Pd(PPh_3)_2Cl_2$, THF, RT, 2h, 99%.

With one of the Stille coupling fragments now in hand, attention turned to the synthesis of the vinyl iodide.

2.2 Synthesis of the vinyl iodide

We required the vinyl iodide to have the two carbon substituents *trans* to each other. Corey has shown[50] that hydroalumination of propargylic alcohols with $LiAlH_4$ is a highly stereoselective process giving rise to *trans*-vinyl alanes which can subsequently be quenched at low temperature with an excess of iodine to give either the β- or γ-vinyl iodide, depending respectively on whether $AlCl_3$ or NaOMe is added to the reducing agent. This methodology was used in the stereospecific synthesis of farnesol (Scheme 34).

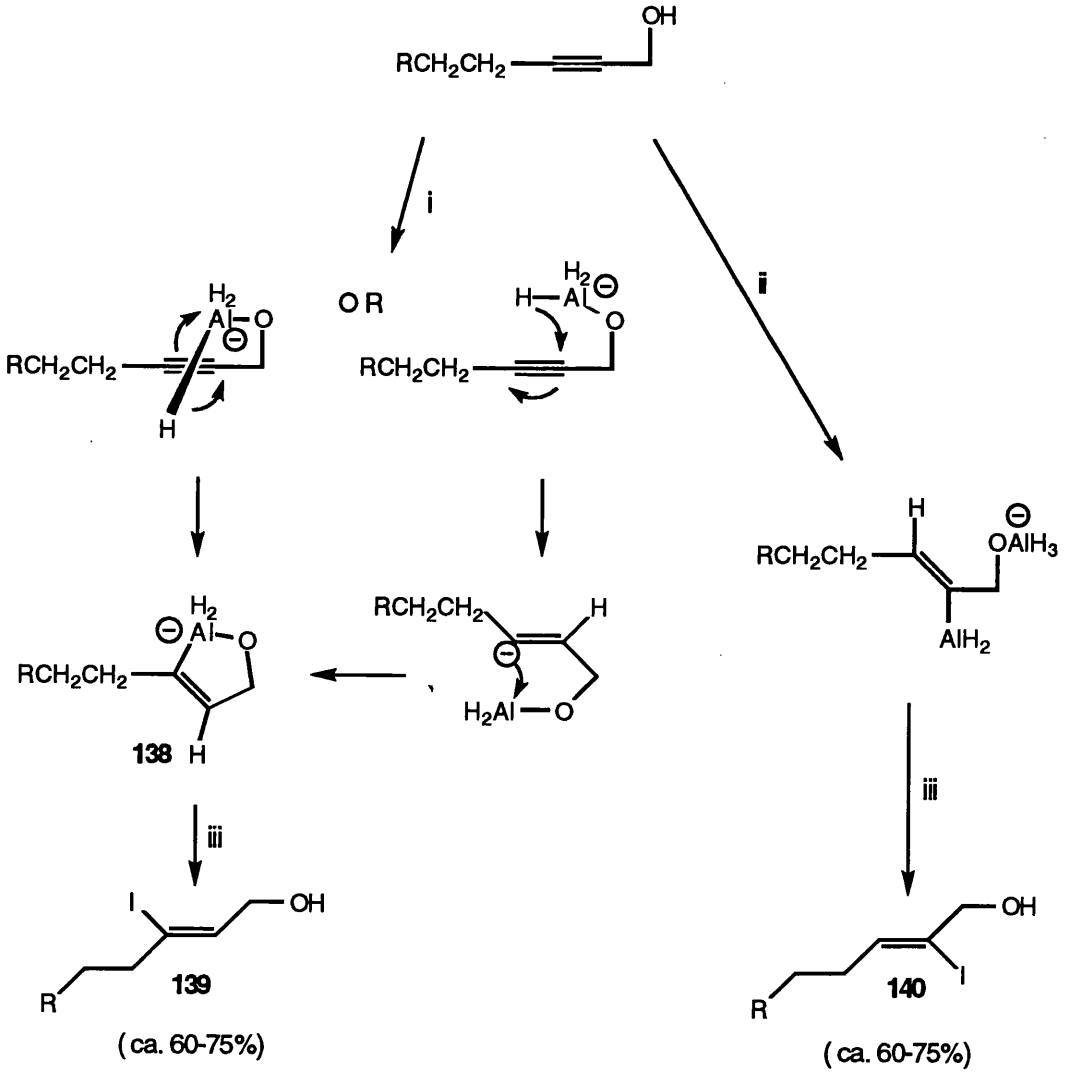


Scheme 34

Reagents and conditions: i) $LiAlH_4$, $AlCl_3$, THF, reflux, 3h then -78°C, I_2; ii) $LiAlH_4$, NaOMe, THF, reflux, 3h then -78°C, I_2.

A possible mechanistic rationale is shown in Scheme 35. The vinylaluminium intermediate **138** is formed by either a concerted or a stepwise intramolecular *trans*-addition to the triple bond. Concerted intramolecular *cis*-addition of an Al-H grouping to an acetylene is geometrically very unfavourable,[51] although hydroalumination using DIBAL-H does involve *cis*-addition of the aluminium-hydrogen bond to the triple bond.[52]

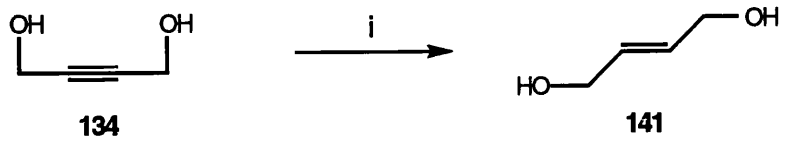
When the organoaluminum intermediate **138** is quenched at low temperature with an excess of iodine, the γ-vinyl iodide **139** is formed in good yield. The reason for the formation of the isomeric β-vinyl iodide **140** when $AlCl_3$ is employed is due to the fact that this reacts with $LiAlH_4$ to generate aluminium hydride (alane) which adds directly to the triple bond in a *trans* fashion rather than through initial coordination with the hydroxyl group.



Scheme 35

Reagents and conditions: i) $LiAlH_4$, NaOMe, THF, reflux, 3h; ii) $LiAlH_4$, $AlCl_3$, THF, reflux, 3h; iii) -78°C, I_2.

The Landor group has shown[53] that hydroalumination of but-2-yne-1,4-diol with $LiAlH_4$ followed by quenching with water gave exclusively the *trans*-isomer of but-2-ene-1,4-diol **141** in 98% yield (Scheme 36).

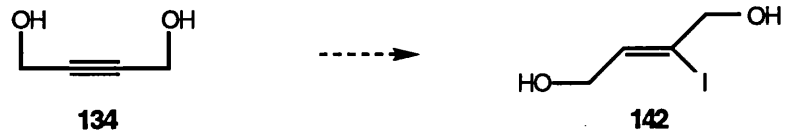


134 **141**

Scheme 36

Reagents and conditions: i) $LiAlH_4$, Et_2O, reflux, 4h; then H_2O, 98%.

It was therefore envisaged that hydroalumination of **134** with $LiAlH_4$ followed by low temperature quench with excess iodine should give rise to the desired *E*-vinyl iodide **142** (Scheme 37).

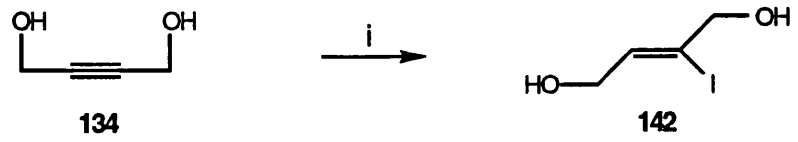


134 **142**

Scheme 37

Initial attempts to synthesise vinyl iodide **142** by heating **134** at reflux in THF with $LiAlH_4$ followed by quenching with excess iodine at -78°C resulted in iodide opening of THF (presumably through aluminium coordination) to give 4-iodo-butan-1-ol as the major product in the crude ^1H NMR. Reducing the amount of $LiAlH_4$ from 2.5 equivalents to 1.6 equivalents eliminated this side reaction. However, although the reaction appeared to proceed relatively well by TLC (which also indicated that hydroalumination was effected completely) the isolated yields of **142** were very disappointing. After addition of I_2, the work up procedure involved quenching the excess $LiAlH_4$ by the successive addition of H_2O/NaOH/H_2O (1:1:3) followed by extraction with ether. It was found that **142** had poor solubility in ether and so EtOAc was later used to extract **142**, though this caused great emulsion problems due to the aluminium salts generated in the quench. However, it was found that this could be minimised by quenching the excess $LiAlH_4$ with dry EtOAc *before*

quenching the organoaluminium species with I_2. Then, after rigorous extraction with EtOAc, the vinyl iodide **142** was obtained in 62% yield (Scheme 38).

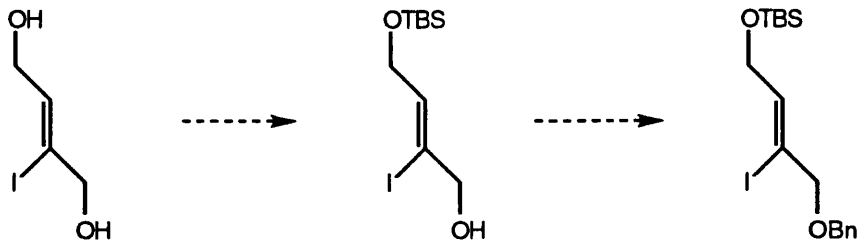


134 **142**

Scheme 38

Reagents and conditions: i) $LiAlH_4$, THF/Et_2O, reflux, 1.5h , then 0°C, anhydrous EtOAc, then -78°C, I_2, 62%.

It was now hoped that good selectivity would be observed for the mono-silylation of **142** to give the mono-protected vinyl iodide **143** which could then be benzylated to give the desired differentially protected vinyl iodide **144** for the Stille coupling (Scheme 39).



142 **143** **144**

Scheme 39

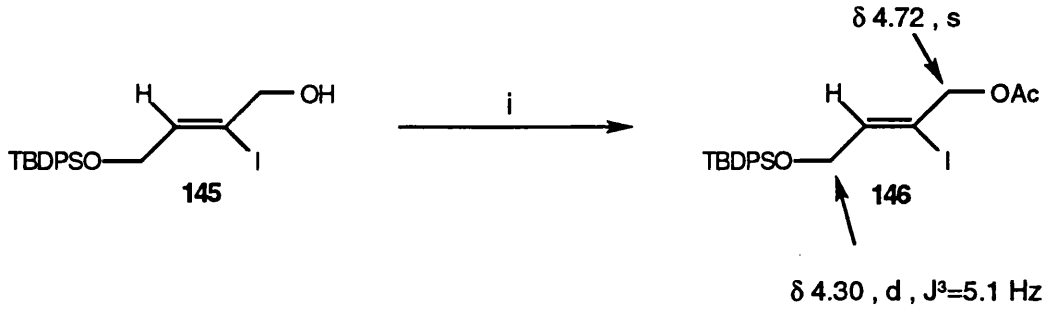
Unfortunately, silylation of **142** with either TBSCl or TBDPSCl under a variety of conditions failed to give any reasonable level of selectivity. The best selectivity observed by TLC analysis was *ca.* 2:1 in favour of the desired regioisomer, and the yields were always low, at best 32%. This was due to three main reasons: competitive bis-silylation, the low levels of conversion used in order to try to reduce bis-silylation, and the difficulty in separating the regioisomers by flash column chromatography (FCC) on a synthetic scale.

The proof of the regiochemistry rests on ^1H NMR evidence. It was thought likely that the J^3 coupling of the alkenic proton to the vicinal CH_2OH would be larger than that to the other allylic methylene. It was also expected that acylation of the primary free hydroxyl would cause downfield shift of the adjacent protons, thus identifying them unambiguously.

Thus, to that end, the major mono-TBDPS protected regioisomer **145** was acylated to give quantitatively **146** (Scheme 40), and the minor mono-TBS protected regioisomer **147** acylated to afford **148** in quantitative yield (Scheme 41).

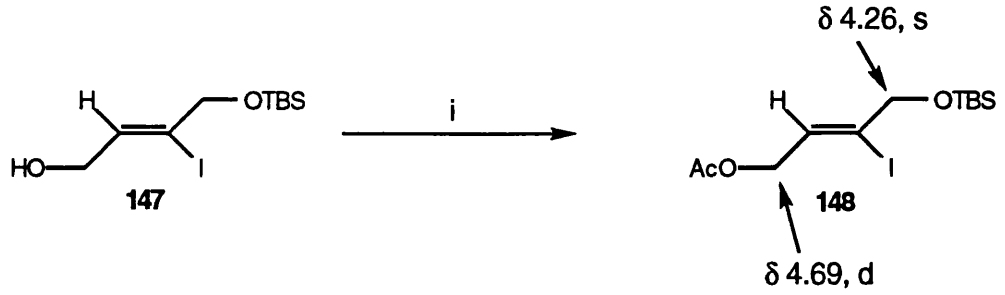
In the ^1H NMR of **146**, the methylene protons next to the acetate group appear at 4.72 ppm as a broad singlet, and the methylene protons next to the silyl ether at 4.30 ppm as a doublet (J = 5.1 Hz) with further fine splitting, confirming the structure of **145**.

In the ^1H NMR of **148** the methylene protons next to the acetate group appear at 4.69 ppm as a doublet consistent for a J^3 coupling, whilst the methylene protons next to the silyl ether at 4.26 ppm appear as a singlet, confirming the structure of **147** and hence by analogy the major regioisomer to be **143**.



Scheme 40

Reagents and conditions: i) Ac_2O, pyridine, CH_2Cl_2, 16h, 100%.

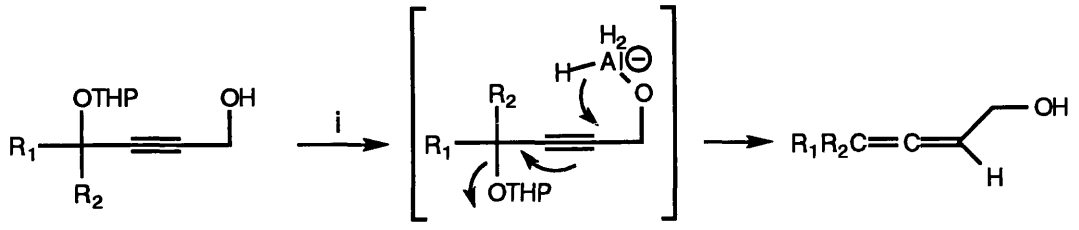


Scheme 41

Reagents and conditions: i) Ac_2O, pyridine, CH_2Cl_2, 19h, 100%.

It was clear that an alternative route was required to access the vinyl iodide due to these protection problems, and it was decided to investigate mono-protection *before* reduction.

Landor had reported that mono-*O*-tetrahydropyran-2-yl derivatives of butyne-1, 4-diols gave rise to α-allenic alcohols when treated with $LiAlH_4$.[53] The mechanism of the reductive elimination step is seen as an intramolecular hydride transfer to C2 with concerted elimination of the tetrahydropyranyloxy group (Scheme 42).

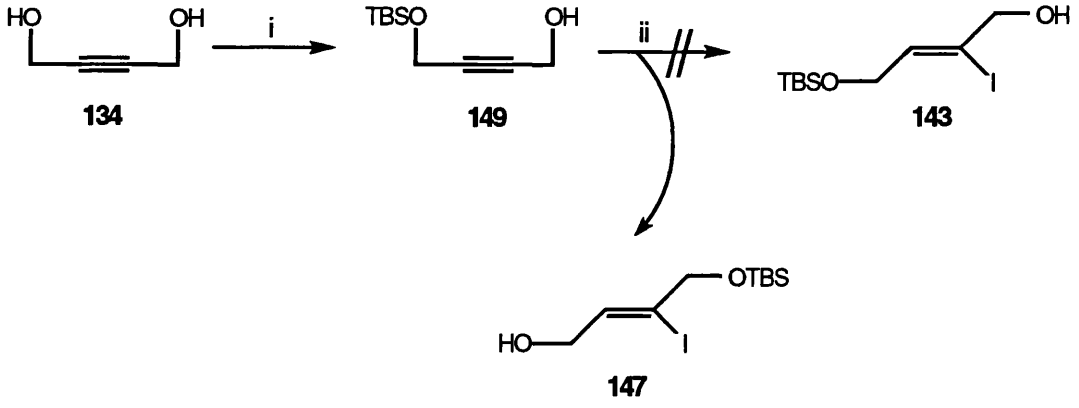


Scheme 42

Reagents and conditions: i) $LiAlH_4$, Et_2O, reflux, then H_2O, 73-95%.

Despite this fact we hoped that if the butyne diol **134** was mono-protected as a silyl ether, it would still be possible to effect hydroalumination followed by quenching with iodine to give a mono-protected vinyl iodide since it was considered that TBDMS ethers are poorer leaving groups than THP ethers due to poorer coordination to $LiAlH_4$.

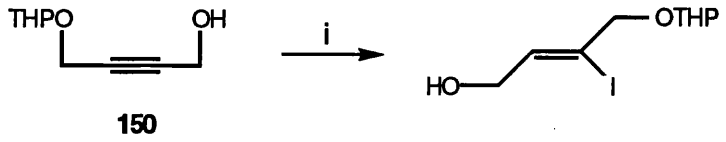
To this end, the mono-TBDMS silyl ether **149** was prepared in 42% yield by treatment of **134** with NaH and TBSCl in DMF. Unfortunately, when **149** was subjected to the $LiAlH_4$ / I_2 procedure, none of the desired regioisomer **143** was detected. However, 2% of the other regioisomer **147** was isolated (Scheme 43) from the complex mixture.



Scheme 43

Reagents and conditions: i) TBSCl, Imidazole, NaH, DMF, 0°C to RT, 42%; ii) $LiAlH_4$, Et_2O, reflux, 1h , then 0°C, anhydrous EtOAc, then -78°C, I_2. 2% of **147**.

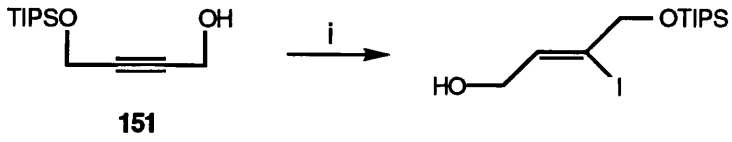
Since it was known that Red-Al™ could also effect *trans*-hydroalumination,[54] the reaction was attempted several times employing Red-Al™ instead of $LiAlH_4$. However, reactions with Red-Al™ gave rise to a complex mixture of at least eight products (according to TLC analysis), none of which were either of the regioisomers **143** or **147**. It was therefore thought that this methodology with the mono-silyl compound also gave rise to the α-allenic alcohol, as the literature suggested, and we turned our attention to a different approach. However, since that time, both Rawal[55] and Overman[56] have successfully carried out this transformation on the THP and TIPS mono-ethers **150** and **151** employing Red-Al, though very little or no experimental conditions were offered (Schemes 44 and 45).



150

Scheme 44

Reagents and conditions: i) Red-Al, Et_2O, 0°C, then I_2.

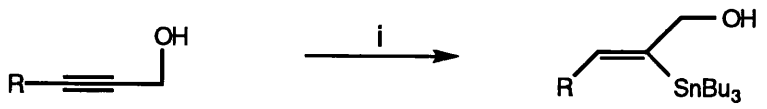


151

Scheme 45

Reagents and conditions: i) Red-Al, then I_2, 88%.

Ensley and co-workers reported that hydrostannylation of disubstituted acetylenic alcohols with $^nBu_3SnH$ / AIBN gave nearly exclusive formation of the *Z*-olefin (Scheme 46) with control of the regiochemistry for propargylic alcohol derivatives.[57]

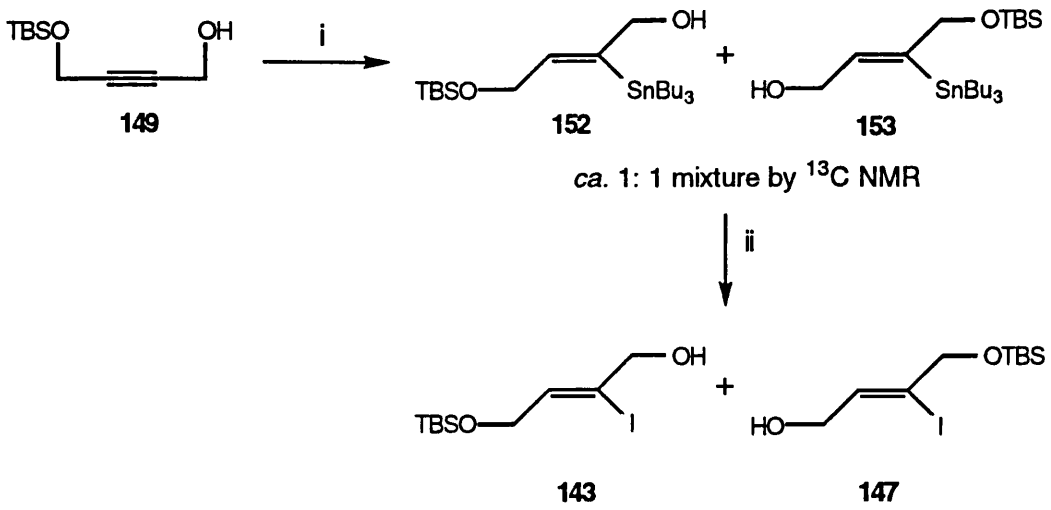


R = Me , C_5H_{11}

Scheme 46

Reagents and conditions: i) $^nBu_3SnH$, AIBN (cat.), 85°C.

It was hoped that treatment of the mono-silyl protected acetylene **149** under these conditions would provide the regioisomer **152** (or even **153** which would still prove useful) which could be converted to the vinyl iodide, since conversion of vinyl stannanes to vinyl iodides with iodine in carbon tetrachloride is known to proceed with retention. However, treatment of **149** with $^{n}Bu_3SnH$ / AIBN at either 85°C or 55°C always gave a *ca.* 1:1 mixture of the regioisomers **152** and **153** (as apparent by the ^{13}C NMR) which co-ran on silica gel in a wide variety of solvent systems and could not be separated (Scheme 47). The stereochemical assignment of **152** and **153** came from conversion to the iodides by treatment with iodine in carbon tetrachloride, and comparison of the ^{1}H NMR spectra of the products with those of the iodides **143** and **147** whose stereochemistry had previously been established on the basis of the mechanism for hydroalumination.



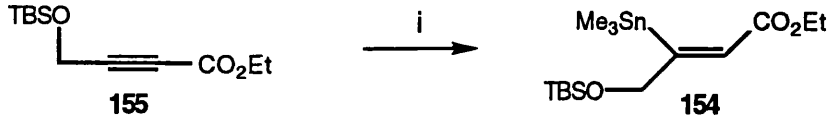
Scheme 47

Reagents and conditions: i) $^{n}Bu_3SnH$, AIBN (cat.), 85°C., 1h 20 min, 89%; ii) I_2, CCl_4, 4°C, 100%.

Although treatment of the mixture of **152** and **153** with I_2 in CCl_4 did quantitatively generate the vinyl iodides **143** and **147**, we already knew that these could not be effectively separated by FCC (see earlier in this section under silylation protection). It was therefore evident that this route was not a viable way forward.

In view of the difficulty encountered in differentiating termini at the alcohol oxidation level, it was decided to start with two electronically different acetylene substituents, whereby one end would be kept at the alcohol oxidation level and the other at the carboxylic acid oxidation level. A compound of this type, vinyl stannane **154**, had been reported by the Piers

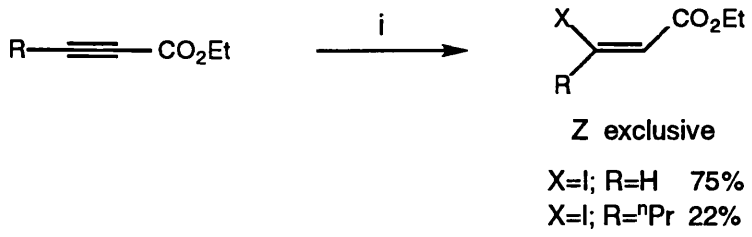
group (Scheme 48).[58] Thus, addition of the higher order cuprate, dilithium(trimethylstannyl)(2-thienyl)(cyano)-cuprate, to the α,β-acetylenic ester **155** in THF at -78°C, was reported to afford a 95:5 mixture of geometric isomers which after FCC provided the *Z*-isomer in 65% yield.



Scheme 48

Reagents and conditions: i) $Me_3SnCu(2\text{-thienyl})(CN)Li_2$, THF, -78°C, 65%.

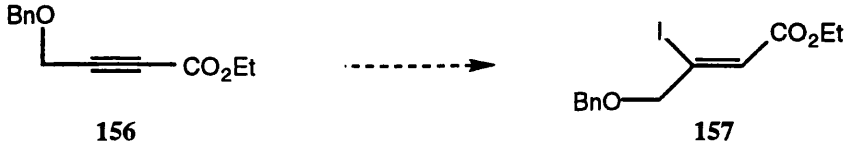
Since vinyl trimethylstannanes are known to be more reactive than the corresponding tributylstannanes in the Stille coupling, it was thought that **154** could be used in the Stille coupling if the previously made vinyl stannane **136** was converted to its corresponding vinyl iodide. However, this route was not examined since a simpler alternative was discovered. Lu and co-workers[59] had reported a novel regio- and stereoselective hydrohalogenation reaction of 2-propynoic acid and its derivatives (Scheme 49). However, Lu reported that 3-substituted-2-alkynoates (R=Pr) afforded poor yields.



Scheme 49

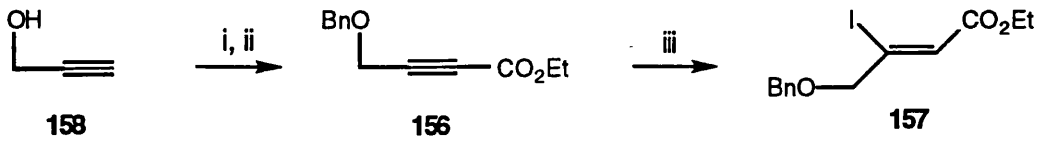
Reagents and conditions: i) LiI, AcOH, 70°C.

It therefore seemed appealing to see if the conjugate addition of LiI to the alkyne **156** would give rise to the desired vinyl iodide **157** (Scheme 50).



Scheme 50

The alkyne **156** was prepared as shown in Scheme 51. Treatment of propargyl alcohol **158** with NaH / BnBr in the presence of catalytic Bu_4NI gave the corresponding benzyl ether in 91% yield. Subsequent treatment with butyl lithium followed by ethyl chloroformate gave the alkynoic ester **156** in 84% yield. To our delight, when **156** was treated with LiI in acetic acid at 70°C it gave exclusively the *Z*-vinyl iodide **157** in virtually quantitative yield after just one and a half hours. This should be contrasted with the work of Lu who had found that the disubstituted acetylene they had tried needed 24h and only gave product in 22% yield.



158 **156** **157**

Scheme 51

Reagents and conditions: i) BnBr, $^nBu_4NI$ (cat.), NaH, DMF, 91%; ii) ^{n}BuLi, THF, -78°C, then $ClCO_2Et$, -78°C to 0°C, 84%; iii) LiI, AcOH, 70°C, 1.5h, 95%.

The stereochemistry of **157** was proven by a combination of ^1H NMR spectroscopy and chemical manipulation. A NOESY experiment showed cross peaks for the vinyl proton and the methylene protons, and nOe difference experiments showed a 15% enhancement of the vinyl methylene protons when the vinyl proton at 6.30 ppm was irradiated. Also the benzylic protons showed a 5% nOe enhancement (Figure 5).

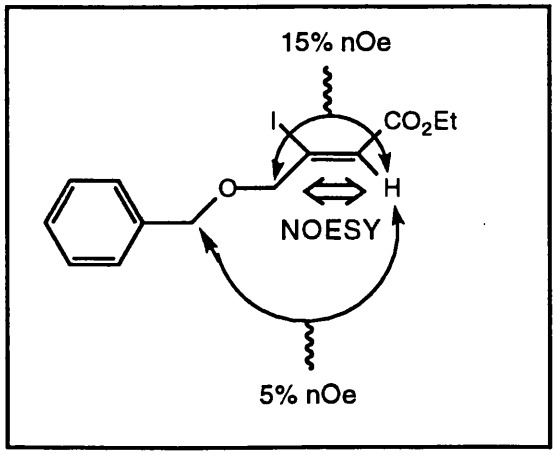
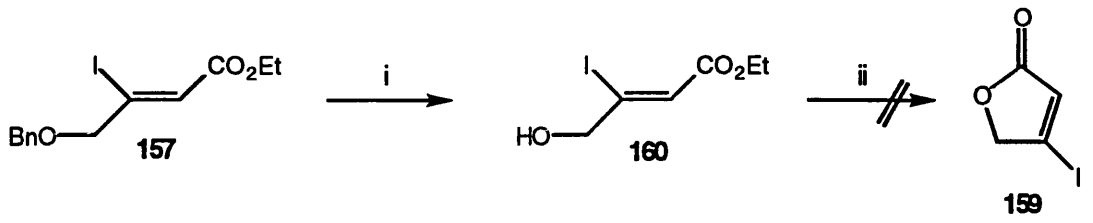


Figure 5: nOe and NOESY experiments for **157**.

It was thought that if we had the wrong stereoisomer, then the debenzylated product should readily lactonise upon acid treatment to give the butenolide **159**. Therefore, **157** was

debenzylated under the Holmes conditions[60] of 7 equivalents $BCl_3 \cdot Me_2S$ to give **160** in 41% yield. This was then subjected to reflux conditions in the presence of tosic acid (Scheme 52). No new products were observed and so this provided further evidence that we had the correct Z-isomer.



Scheme 52

Reagents and conditions: i) $BCl_3 \cdot SMe_2$, CH_2Cl_2, 41%; ii) *p*-TsOH (cat.), CH_2Cl_2, reflux, 3h.

With the two stereodefined alkenes now in hand, attention focused on the Stille coupling.

2.3 The Stille coupling reaction

To obtain the geometrically pure 1,3-diene, a stereospecific carbon-carbon bond forming reaction was required. Carbon-carbon bond formation is one of the most critical operations in organic synthesis yet there are relatively few fundamental methods available. It has been known for some time that Group VIII transition metals, particularly Ni and Pd, effectively catalyse the cross-coupling of organometallic reagents with organic halides and related electrophiles (Eq. 1).

$$RM + R'X \xrightarrow{M'} R\text{-}R' + MX$$

Eq.1

However, many of the organometallic reagents available are sensitive to the functionality on the coupling partners and are often difficult to prepare or are air or moisture sensitive, and few can be purified and stored.

Organolithium or Grignard reagents usually give poor conversion and often homocoupling of the organic halide is observed. They also have a low tolerance for functional groups.

Although coupling of organocopper alkenyl or aryl compounds give higher conversions, they suffer from extensive homocoupling. Moreover, the synthetic methods available for organocopper reagents tend not to allow the presence of more reactive functional groups on the organocopper partner.

Organometallic reagents containing metals of intermediate electropositive character such as zinc or mercury generally lead to higher yields of coupled product and fewer side reactions since they both tolerate a wide range of functional groups in either of the coupling partners. However, methods for their synthesis are somewhat limited.

The structure of the organic portion in organoboranes or aluminiums is also limited by the methods of synthesis available, namely hydroboration or hydroalumination.

Organozirconium reagents have the advantage of compatibility with ether or acetal groups, along with carbonyl and ester groups (if in the alkenyl halide partner) but suffer from low catalytic turnover.

However, organotin reagents must be easily one of the most versatile organometallic reagents in Pd-catalysed coupling reactions. They are compatible with a wide variety of reactive functional groups, there is a reasonably large number of methods for their preparation, and they are not particularly oxygen or moisture sensitive.

In the Pd-catalysed coupling of electrophiles with organotin reagents, only one of the groups on the tetravalent tin is transferred. Fortunately, different groups are transferred from tin with different rates, the simple alkyl group being slowest:

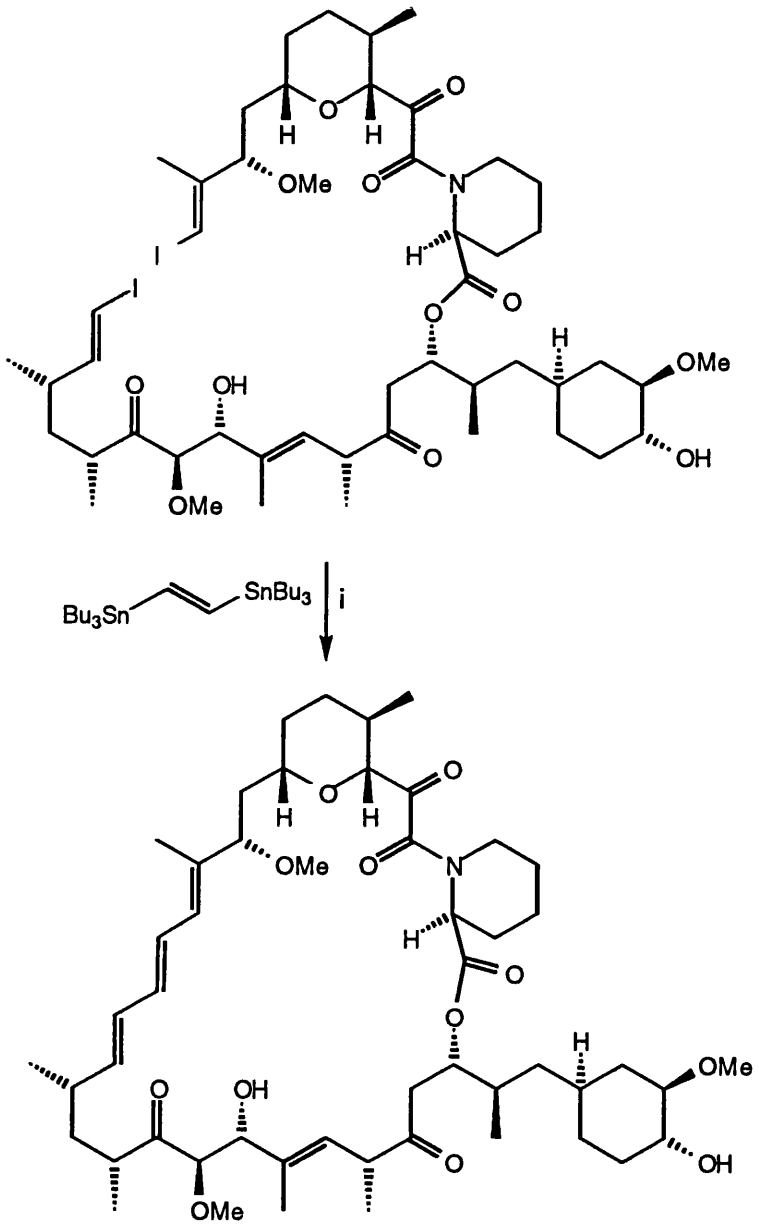
$$R{-}{\equiv} > RCH{=}CH > Ar > RCH{=}CHCH_2 \approx ArCH_2 > CH_3COCH_2 > C_nH_{2n+1}$$

$$RX + R'SnR''_3 \xrightarrow{[\,PdLn\,]} R\text{-}R' + XSnR''_3$$

Eq.2

Thus, three simple alkyl groups (such as methyl or butyl) are used and the fourth group on tin, which undergoes transfer, can be an alkyl, alkenyl, aryl, benzyl, alkynyl or allyl group.

This palladium catalysed cross-coupling reaction of an organotin reagent with organic electrophiles (Eq.2) has become commonly known as the Stille coupling, after J. K. Stille.[47] It is a mild, versatile reaction, tolerant of functionality on either coupling partner, and moreover it is stereospecific and regioselective, giving product in high yields. This makes it ideal for the use in the synthesis of elaborate organic molecules. An impressive recent example is in the synthesis of rapamycin by the Nicolaou group (Scheme 53).[61]

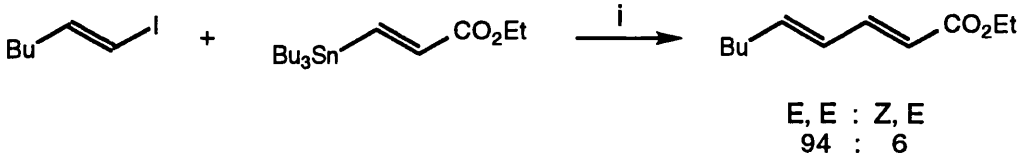


Scheme 53

Reagents and conditions: i) 20 mol% $Pd(MeCN)_2Cl_2$, $^iPr_2EtN$, DMF/THF (1:1), RT, 24h, 28%.

A wide variety of both electrophile and organotin reagents can be coupled. The following examples illustrate the scope and versatility of this reaction and highlight the compatibility of functional groups.

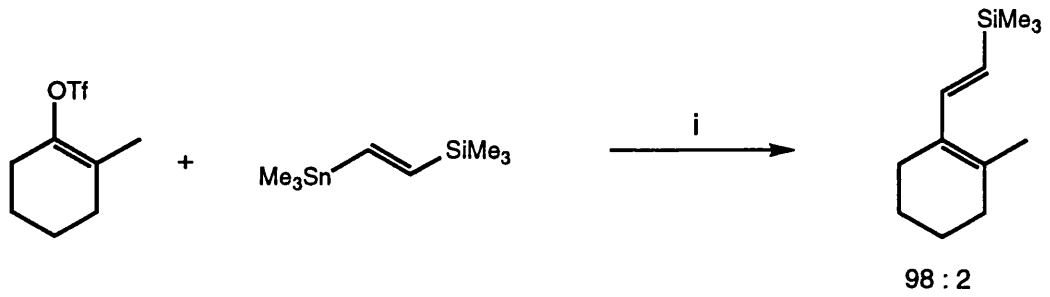
Substituted vinyl halides undergo direct Pd-catalysed cross-coupling with alkenyltin reagents to give good yields of conjugated dienes. The reaction proceeds with retention of double-bond configuration in both vinyl partners (Scheme 54).[62] Vinyl iodides react readily at 25°C-40°C, whilst vinyl bromides require higher temperatures (100°C) for the oxidative addition step to take place readily.



Scheme 54

Reagents and conditions: i) $Pd(MeCN)_2Cl_2$, DMF, RT, 83%.

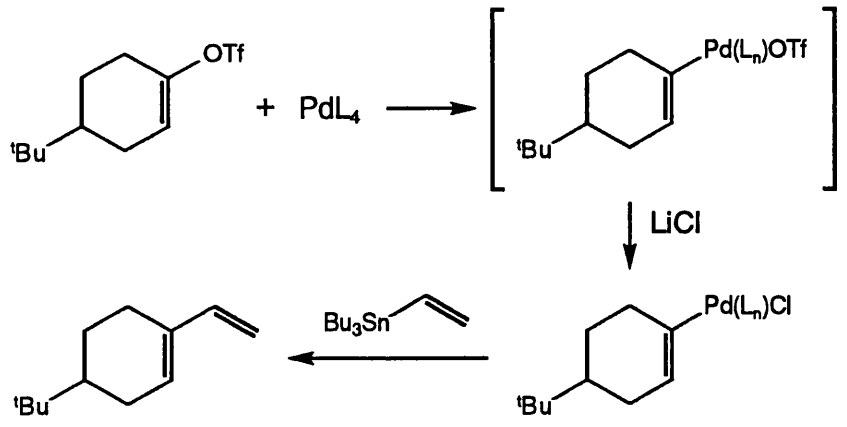
Vinyl triflates can be made to undergo Pd-catalysed couplings provided that LiCl is added to the reaction mixture (Scheme 55).[63] The coupling of vinyl triflates is particularly valuable due to the ease of their selective synthesis from unsymmetrical ketones by generating either the kinetic or thermodynamic enolate.



Scheme 55

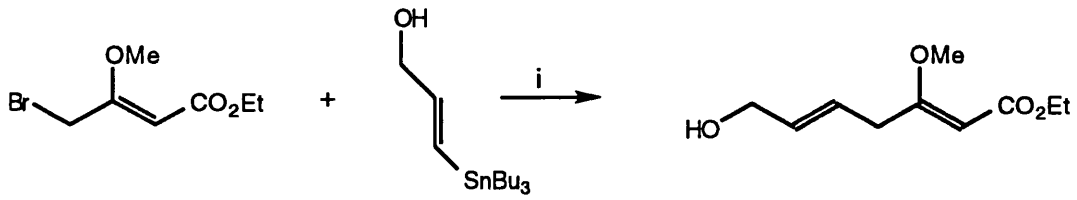
Reagents and conditions: i) $Pd(PPh_3)_4$, LiCl, DMF, RT, 90%.

The LiCl is required to form the vinyl palladium chloride complex since palladium triflates will not undergo intermolecular transmetallation with vinyl tin compounds (Scheme 56). Examples of intramolecular couplings where LiCl is not a prerequisite have been reported, however.[64]



Scheme 56

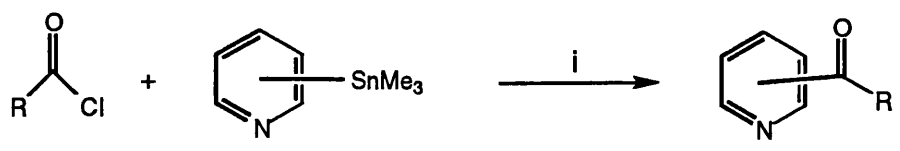
The coupling of allyl bromides or chlorides with alkenyl or aryl tin reagents leads to 1,4-dienes in high yields, such as the example in Scheme 57[65], and proceeds with retention of double bond geometry in both coupling partners. The allyl halide undergoes regioselective coupling at the primary allylic carbon, and hence the process exhibits stereospecific and regioselective sp^2-sp^3 coupling.



Scheme 57

Reagents and conditions: i) 3 mol% $Pd_2(dba)_3$, 6 mol% PPh_3, THF, 50°C, 82%.

The coupling of organotin reagents with acid chlorides allows for the synthesis of ketones. The coupling is quite general with respect to both the acid chloride and the organotin partners. For example, the Stille coupling has been used in a novel C-C bond formation on pyridine nuclei (Scheme 58).[66]



Scheme 58

Reagents and conditions: i) $Pd(PPh_3)_2Cl_2$, PhH, reflux, 8-10h.

The currently accepted mechanism[47] for the Stille coupling involves three basic steps (Figure 6) : 1) Oxidative addition; 2) Transmetallation; 3) Reductive elimination.

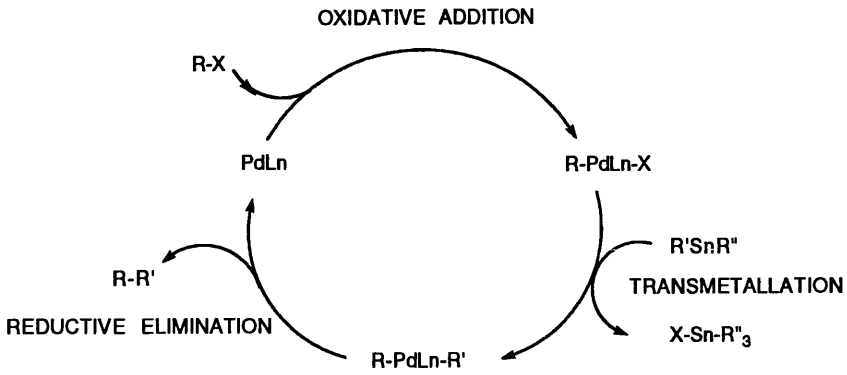
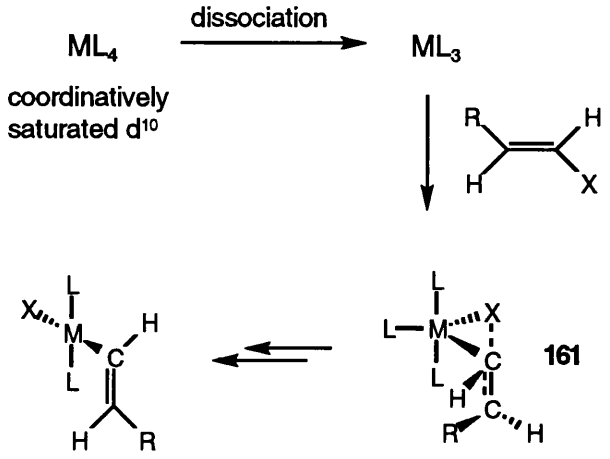
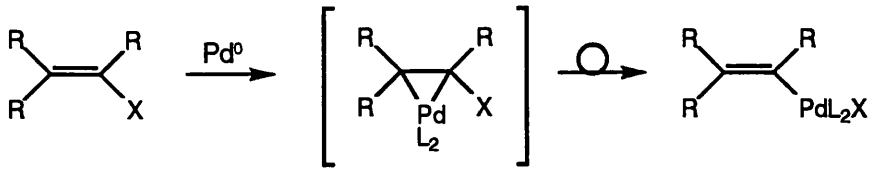


Figure 6: Mechanism of the Stille coupling

The oxidative addition of vinyl halides to palladium complexes affords stable σ-vinyl Pd complexes. The process is stereospecific as the configuration at the trigonal carbon bearing the halogen is retained in the oxidative addition product. In order for the oxidative addition to take place the palladium must be in the zerovalent state, usually stabilised by ligands. The oxidative addition process is believed to proceed in one of two ways: either *via* a dissociative mechanism where loss of a ligand may result in a coordinatively unsaturated species ML_3 which leads to a five-coordinate transition state **161** arising from nucleophilic attack of Pd on the carbon halogen bond (Scheme 59), or *via* a three membered pallada cycle **162** which rearranges to the σ-vinyl Pd complex (Scheme 60).



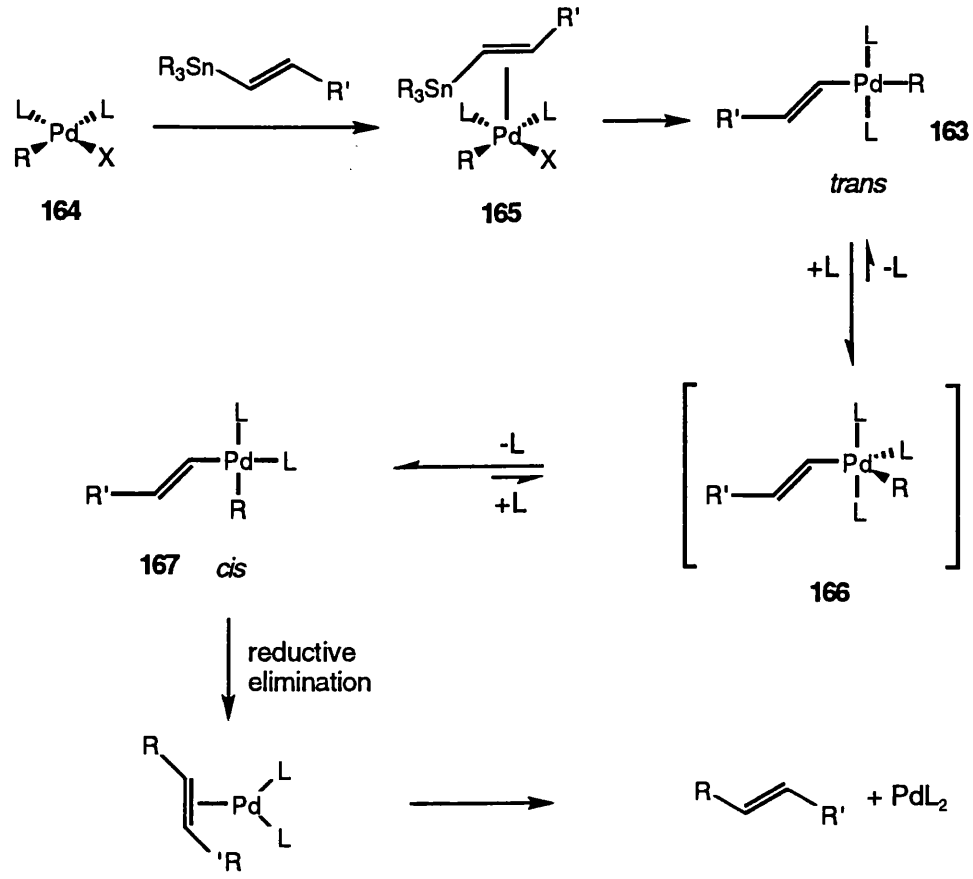
Scheme 59



162

Scheme 60

The next step in the process is the transmetallation. The original ideas on the mechanism of this step are shown in Scheme 61.[47] The transmetallation was thought to proceed to the *trans*-Pd(II) complex **163** from the coordinatively saturated species **164** *via* a pentacoordinate Pd(II)-π-stannyl complex species **165**, though the exact nature of **165** was unknown. Following the transmetallation step, a *trans*- to *cis*-isomerisation takes place *via* a five-coordinate transition state such as **166**, which undergoes pseudorotation and dissociation of a ligand to give the *cis*-Pd(II) complex **167**. For the subsequent 1,1-reductive elimination it was discovered that the groups to be coupled must occupy the *cis* positions. Isolated *trans*-Pd(II) intermediates did not undergo reductive elimination in non-polar solvents. It was found that a polar coordinating solvent was necessary for the isomerisation of the *trans*-complex to the *cis*-complex to take place. For this reason, polar coordinating solvents such as DMF, THF and NMP are used in Stille couplings, the most effective being reported to be the highly dipolar coordinating NMP.[62, 67]



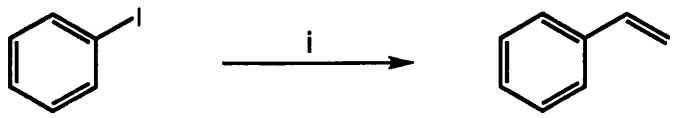
Scheme 61

It is now generally accepted that the transmetallation is the rate-determining step in most cross-couplings of synthetic interest. Though initially not well understood, efforts directed at this transmetallation step have led to a greatly increased understanding as to how this reaction might be operating and the earlier mechanistic picture described above has been modified. This has consequently led to significantly useful modifications of the reaction conditions which have now found widespread use in this cross-coupling area (*vide infra*).

2.3.1 Catalyst systems for the Stille cross-coupling

Different catalysts have been compared,[64] and until recently the preferred catalyst for Stille couplings was usually $Pd(PPh_3)_4$. However, it was observed that excess phosphine retarded the coupling and this led to the use of the coordinately unsaturated catalyst "$Pd(PPh_3)_2$" , usually obtained *in situ* from a Pd(II) species.

However, the most significant findings of recent years have been from Farina and co-workers. They discovered a very substantial ligand effect in a model coupling between iodobenzene and vinyltributyltin (Scheme 62) and showed that this kind of effect is general for a variety of Stille couplings.[68] In general, ligands of low donor capabilities are associated with fast rates, whereas strong donor ligands, such as the traditional PPh_3, are inhibitors of the reaction. After screening a series of ligands, Farina's studies uncovered two new useful ligands for Stille cross-coupling chemistry (Table 5). It was found that by using P(2-furyl)$_3$ or Ph_3As as the ligand instead of PPh_3, a 100 or 1000-fold rate increase was observed respectively for the coupling of vinyl stannanes with vinyl / aryl iodides or vinyl triflates. It was found that the optimum ratio of Pd : Ligand was 1:2 for P(2-furyl)$_3$ and 1:4 for As_3P when generated from the weakly coordinated $Pd_2(dba)_3$ catalyst.



Scheme 62

Reagents and conditions: i) CH_2=CHSnBu_3, $Pd_2(dba)_3$, Ligand, THF, 50°C

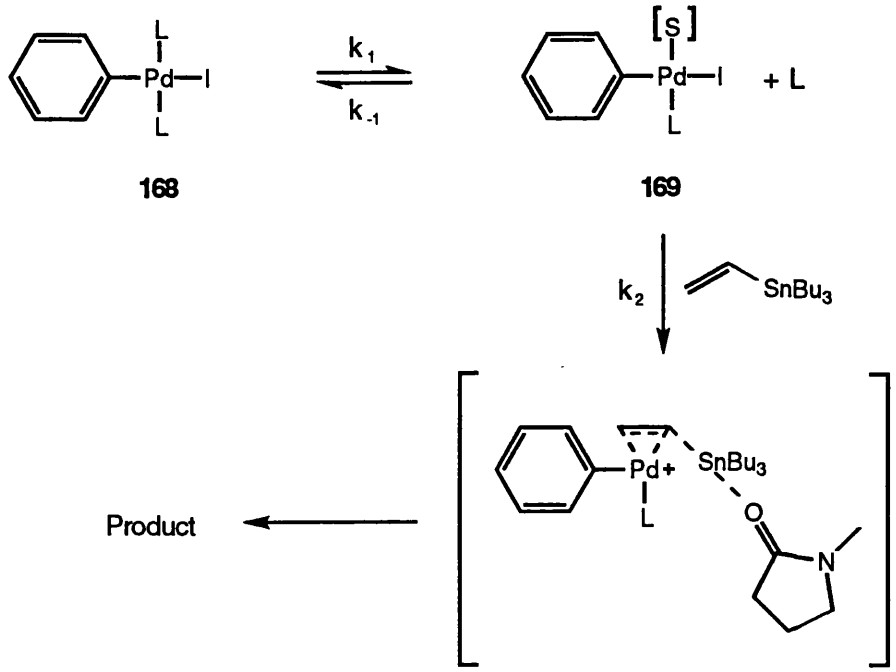
Table 5: Summary of Ligand effects in the Stille reaction

Ligand	Rel k_{obs}	Inhib. Factor‡
(*p*-MeO-C_6H_5)$_3$P	< 0.07	> 100
PPh_3	1.0	19
(2-furyl)$_3$P	105	3.7
$AsPh_3$	1100	1.3

‡Inhibition factor of excess ligand

It is thought that these ligands work by accelerating the rate of the transmetallation step *via* ligand dissociation and formation of a Pd-stannane π-complex. Prior to Farina's work, it was believed that the fully coordinated species **168** was involved in the transmetallation step. Kinetic studies by Farina[68] have led to a new model which proposes a

pre-equilibrium between fully coordinated species **168** and a coordinatively unsaturated intermediate **169** as depicted in Scheme 63.



Scheme 63

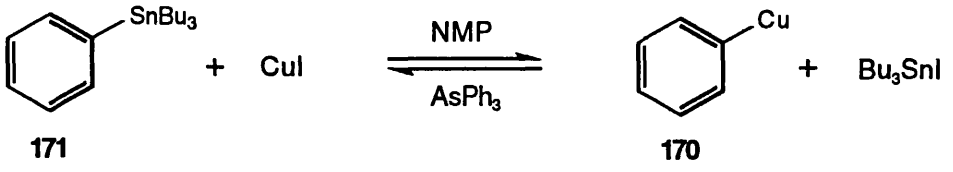
Ligands of high donicity (eg. PPh_3) inhibit the reaction because they allow only minute concentrations of the reactive species **169** at equilibrium. Although substitution reactions at square planar Pd(II) complexes usually proceed associatively *via* pentacoordinated intermediates (as in Scheme 61), Farina's kinetic studies suggest that in the case where the nucleophile is an organostannane, the Pd(II) electrophile must be coordinatively unsaturated to engage in transmetallation. The low donicity of the $(2\text{-furyl})_3P$ and $AsPh_3$ ligands facilitate their dissociation from palladium favouring the coordinatively unsaturated species at equilibrium and hence leading to increased reactivity.

Another approach to increasing the rate of transmetallation has been the addition of a second metal salt. 1,1- and 1,2-Disubstituted alkenyl-2-metallics are reported to react unsatisfactorily in Pd-catalysed reactions in the absence of $ZnCl_2$ or $CdCl_2$.[64, 69] It was initially thought that addition of $ZnCl_2$ results in transmetallation from the organotin to provide the corresponding organozinc chloride. However, Farina reported that the use of anhydrous $ZnCl_2$ in a strictly anhydrous atmosphere offered no rate enhancement of the coupling reaction compared to the same reaction without $ZnCl_2$, but that use of $ZnCl_2$

directly from the bottle gave a 2 to 3-fold rate increase.[67] Farina therefore deduced that the beneficial effect of adding $ZnCl_2$ to the reaction may be due to its water of hydration or to traces of hydrogen chloride.

Another common approach to enhance reactivity and sometimes selectivity in the Stille coupling has been the use of co-catalytic copper(I), as first introduced by Liebeskind in 1990.[70] More recently, Farina, in collaboration with Liebeskind, has begun to study the mechanistic basis of this effect.[71] Their initial data suggest that Cu(I) acts as a "phosphine scavenger" in these couplings. Since ligand dissociation from **168** (Scheme 63) is a key event in the transmetallation, any secondary metal ion with an affinity for phosphines may help shift this pre-equilibrium toward **169**. It is thought that this is how CuI can provide up to a 100-fold acceleration when PPh_3 is used as a ligand, although addition of CuI in conjunction with low donicity ligands such as $AsPh_3$ is essentially ineffective.

Farina and Liebeskind have ^{119}Sn NMR data to suggest that a second effect becomes important when, and only when, working in the highly dipolar NMP solvent. Their data showed that aryl and alkenyl stannanes react with CuI in NMP in the presence of "soft" ligands like $AsPh_3$ to afford an apparent equilibrium which they presumed contained an organocopper species **170** (Scheme 64).



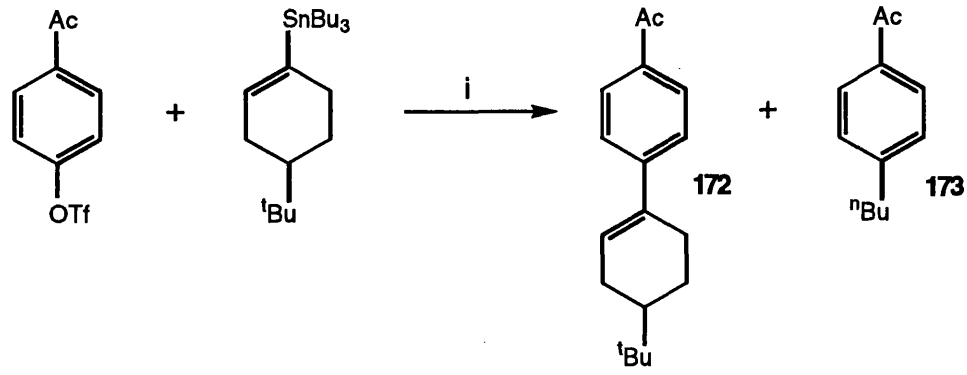
171 **170**

Scheme 64

They proposed that the non-polar stannane **171** is cleaved to a trialkyl tin halide, which is strongly stabilised in NMP through pentacoordination, and that this might constitute a substantial enough thermodynamic contribution to favour the organocopper species.

In addition to kinetic accelerations, the Sn/Cu transmetallation has been reported to effect the selectivity of the coupling. Although methyl and butyl groups at tin are usually innocent bystanders, several cases have been reported where they can compete with more reactive moieties in the transfer reaction onto Pd(II). Scheme 65 illustrates this case where

although switching to the $AsPh_3$ ligand greatly reduced the undesired butyl transfer, addition of 5mol% CuI gave rise to virtually exclusive alkenyl transfer.[72]

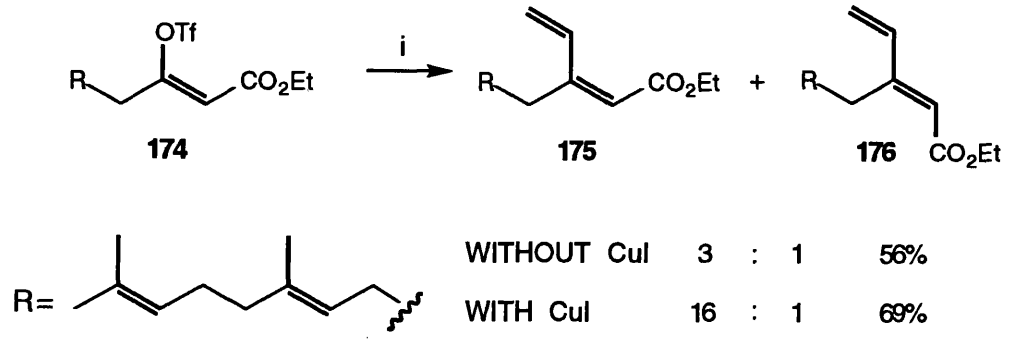


Reagents and conditions: i) 2% $Pd(PhCN)_2Cl_2$, LiCl, NMP, 80-100°C, 8% ligand.

Ligand	Temp °C/Time	172:173
$(2\text{-furyl})_3P$	100°/5h	64:36
$AsPh_3$	80°/7h	90:10
$AsPh_3$ + 5% CuI	80°/6h	>98:2

Scheme 65: Group transfer selectivity enhancement in the Stille reaction by co-catalytic copper

The benefit of co-catalytic Cu(I) on the stereoselectivity of the reaction has been reported by Gibbs and co-workers.[73] Coupling of vinyl triflate **174** with vinyltributyltin using $Pd(PPh_3)_4$ in THF at reflux afforded a 1:1 mixture of dienic esters **175** and **176**. Use of "$Pd(AsPh_3)_2$" in NMP increased the ratio to 3:1, but addition of 10 mol% CuI dramatically increased the stereoselectivity to 16:1 in addition to increasing the yield (Scheme 66).



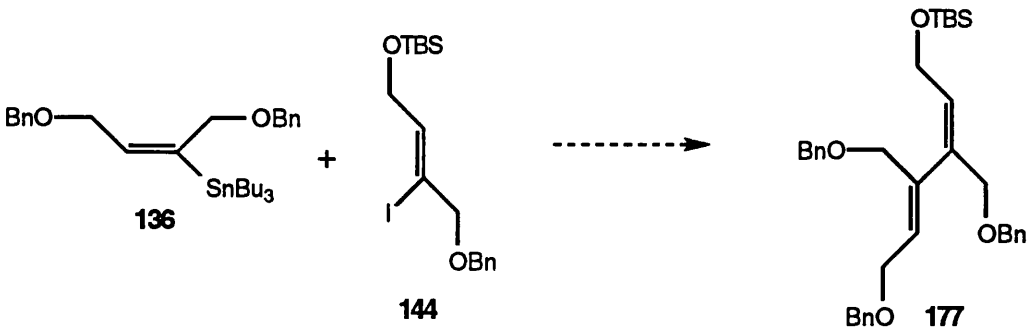
Scheme 66

Reagents and conditions: i) $Pd(AsPh_3)_2$, NMP, RT.

It is clear that the Stille coupling is actually a family of related reactions. In each one, the transmetallation proceeds in a fundamentally unique fashion and is subject to unique effects by ligands and additives.

2.4 Synthesis of the 1,3-diene

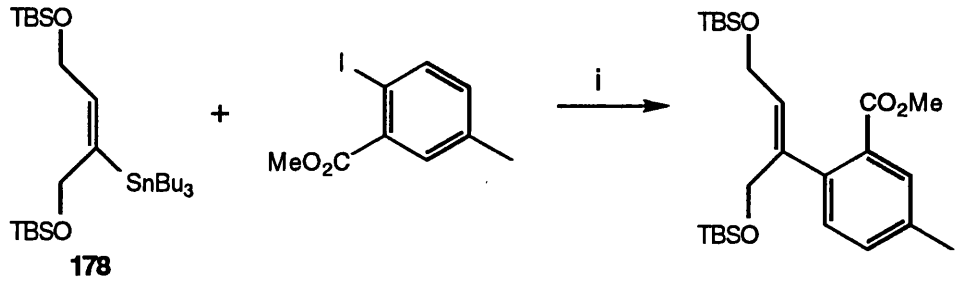
In our synthesis we required the coupling of the vinyl stannane **136** with the differentially protected vinyl iodide **144** to give the 1, 3-diene **177** as shown in Scheme 67.



Scheme 67

However, since the differentially protected alkene **144** proved initially elusive it was decided preliminarily to subject diol **142** (obtained from the hydroalumination and iodine quench procedure) and **136** to the Stille coupling as a test of the methodology, since it was known that the Stille coupling tolerated unprotected hydroxyl functionality.

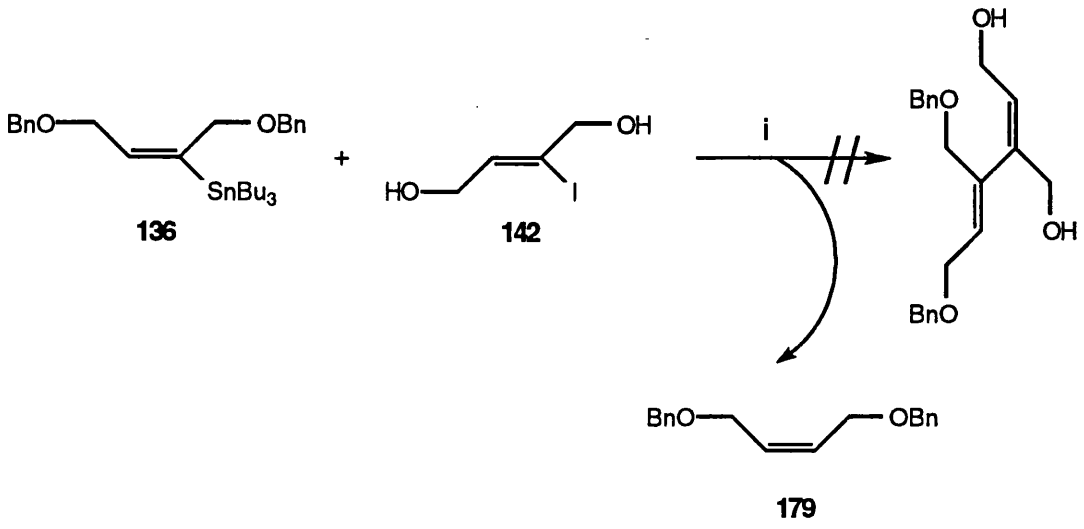
Kocienski[74] had reported a Stille coupling employing the bis-TBS ether protected analogue **178** of stannane **136** (Scheme 68), and so the same conditions were employed.



Scheme 68

Reagents and conditions: i) 8 mol% $Pd(PPh_3)_2Cl_2$, $ZnCl_2$ (2 eq), LiCl (2 eq), dioxane, reflux, 48h, 43%.

Thus, the vinyl iodide **142** and vinyl stannane **136** were heated under reflux in 1,4-dioxane with 2 equivalents of $ZnCl_2$ and LiCl in the presence of Pd (0) (Scheme 69). LiCl was added to the reaction, as although there is no vinyl triflate involved, Kocienski had suggested it aided catalyst stability.[74] However, the main product was **179**, resulting from protodestannylation of **136** . Other materials recovered were an inseparable complex mixture containing the starting vinyl iodide **142** and various catalyst derivatives. The crude ^1H NMR showed only small amounts of coupled product.

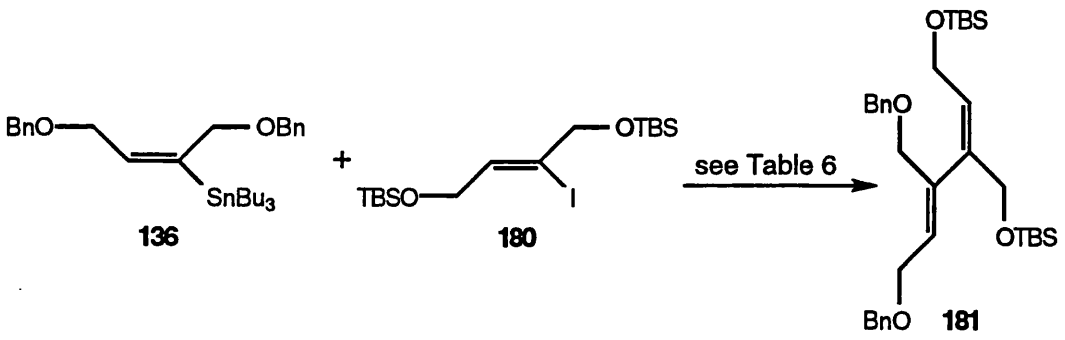


Scheme 69

Reagents and conditions: i) 8 mol% $Pd(PPh_3)_2Cl_2$, $ZnCl_2$ (2 eq), LiCl (2 eq), dioxane, reflux.

The next attempt at the coupling was using the vinyl iodide **144** derived from **143**. However, this time some of the reaction conditions were changed. Since DMF and NMP had been reported to be the solvents of choice for Stille cross couplings,[62, 67] the reaction was carried out in DMF rather than 1,4-dioxane. It was thought that the protodestannylation of **136** might be as a result of the elevated temperature of 1,4-dioxane at reflux and/or the addition of the $ZnCl_2$, and so the reaction was performed at room temperature with the omission of the $ZnCl_2$. The same Pd catalyst was employed, but the reaction was performed in the dark since the Pd catalyst is light sensitive. However, these less severe conditions gave no coupled product at all even after several days.

Due to the shortage of **144** at this time, the plentiful bis-silyl ether protected vinyl iodide **180** became our test substrate for investigating the coupling reaction (Scheme 70). The results are shown in Table 6.



Scheme 70

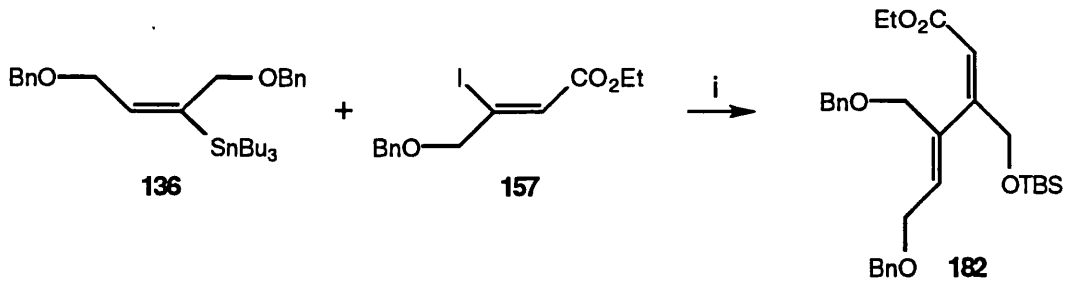
Table 6: Results of Stille coupling of **136** and **180**

Entry	*Reagents and conditions:*	*Results*
1	$Pd(PPh_3)_2Cl_2$, DMF, RT, N_2, DARK	No product
2	$Pd(PPh_3)_2Cl_2$, DMF, RT, N_2, DARK, ultrasonication	No product
3	$Pd_2(dba)_3$, DMF, RT, N_2, DARK	No product
4	$Pd(MeCN)_2$, DMF, RT, N_2, DARK	No product
5	$Pd_2(dba)_3$:P(2-furyl)$_3$ (1:4), DMF, RT, N_2, DARK	No product
6	$Pd_2(dba)_3$:P(2-furyl)$_3$ (1:4), DMF, 70°C, N_2, DARK, 3.5d	8% **181**
7	$Pd_2(dba)_3$:P(2-furyl)$_3$ (1:2), 2eq $ZnCl_2$, degassed DMF, 88°C, N_2, DARK, 24h	27% **181** + 29% **179**

Our starting point in seeking the optimum conditions were those mentioned above for vinyl iodide **144**. As entry 1 shows, no coupled product was observed. It was thought that a change in catalyst might be beneficial, but again, as entries 2-5 show, no reaction was observed with a variety of catalysts at room temperature or when ultrasonication was employed. Even the Farina conditions at room temperature failed to give any coupled product (entry 5).

It was not until the reaction was heated that any coupled product was observed (entry 6). This observation highlighted the reluctance of this reaction to proceed under mild conditions, and so in the following attempt not only was the temperature elevated, but also a more active catalyst ratio was employed, along with the addition of 2 equivalents of $ZnCl_2$ (to help effect transmetallation). Additionally, the solvent was degassed prior to use. As entry 7 shows, this gave diene **181** in 27% yield, but also 29% of the destannylated alkene **179** which was probably as a result of the prolonged elevated temperature (as was the case in our initial experiment with vinyl iodide **142** employing the same conditions used as Kocienski (see Scheme 69)).

By this time we had prepared vinyl iodide **157** and it was submitted to the same conditions as entry 7 (Table 6), only with the temperature lowered to 50°C to try to reduce the unwanted protodestannylation. To our delight this gave the dienic ester **182** in a reasonable 50% yield in the first attempt (Scheme 71). After this pleasing result, a series of experiments was run in order to optimise the yield of the reaction, the results of which are summarised in Table 7.



Scheme 71

Reagents and conditions: i) 2 mol% $Pd_2(dba)_3$, 4 mol% P(2-furyl)$_3$, $ZnCl_2$ (2 eq), DMF, 50°C, 21h, 50%.

Table 7: Stille coupling optimisation of **136** and **157**.

Entry	*‡Reagents and conditions*	*diene 182 (%)*
1	2% $Pd_2(dba)_3$, 4% P(2-furyl)$_3$, 2eq $ZnCl_2$, DMF, C=1, 50°C, 21h	50%
2	5% $Pd_2(dba)_3$, 10% P(2-furyl)$_3$, 10% CuI, 2eq $ZnCl_2$, DMF, C=3, 50°C, 20h	49%
3	2% $Pd_2(dba)_3$, 4% P(2-furyl)$_3$, 4% CuI, DMF, C=1, 50°C, 4.5d	10%
4	1% $Pd_2(dba)_3$, 2% P(2-furyl)$_3$, 2eq $ZnCl_2$, DMF, C=1, 50°C, 2.75d	55%
5	2% $Pd_2(dba)_3$, 4% P(2-furyl)$_3$, 2eq $ZnCl_2$, NMP, C=2, 50°C, 5.5d	57%
6	2% $Pd_2(dba)_3$, 8% $AsPh_3$, NMP, C=1, 1d at RT then 3d at 50°C	68%
7	2% $Pd_2(dba)_3$, 8% $AsPh_3$, 2eq $ZnCl_2$, NMP, C=1, 3d at RT then 28h at 50°C	17%
8	2% $Pd_2(dba)_3$, 8% $AsPh_3$, 8% CuI, NMP, C=1, 1d at RT then 7d at 50°C, DARK	50%
9	2% $Pd_2(dba)_3$, 4% P(2-furyl)$_3$, 2eq $ZnCl_2$, DMF, C=1, 50°C, 3.5d	77%
10	2% $Pd_2(dba)_3$, 4% P(2-furyl)$_3$, 2eq $ZnCl_2$, DMF, C=1, 50°C, 4.5d	86%
11	***2% $Pd_2(dba)_3$, 4% P(2-furyl)$_3$, 2eq $ZnCl_2$, DMF, C=1, 50°C, 16h***	***83%***

‡ C=relative concentration, solvents degassed and reactions performed under N_2.

In order to improve on entry 1, changes were applied to several variables that were thought likely to offer some improvement to the reaction. As mentioned previously, addition of co-catalytic amounts of copper(I) had been reported to be beneficial in particularly difficult Stille couplings. Therefore, the second attempted reaction (entry 2) was pushed by addition of more catalyst and CuI as co-catalyst aswell as increasing the reaction concentration three-fold. It initially seemed that the best conditions had been met as judged by the rate of consumption of starting materials. All starting materials had been consumed within 20h (TLC) but the isolated yield of the diene was only a disappointing 49% (entry 2).

Although these conditions initially led to a substantial rate enhancement, they would appear to suffer from reduced catalyst stability.

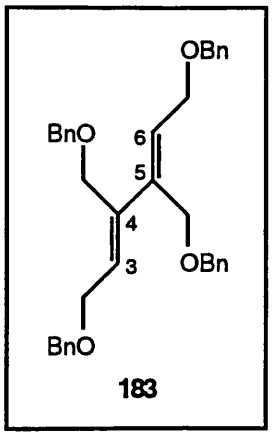
The following experiment omitted the $ZnCl_2$ and the reaction yield fell drastically to 10%, highlighting the beneficial use of added $ZnCl_2$ (entry 3). Entry 4 versus entry 1 shows that reduced amounts of catalyst require longer reaction times to obtain the same yields. Use of NMP (entry 5) instead of DMF appeared to require considerable lengths of time to achieve the same result as entry 1 (albeit the reaction concentration was doubled). By this stage the reaction yield was still not satisfactory and so the $AsPh_3$ ligand was employed in the next attempt since Farina had reported it to be superior to the P(2-furyl)$_3$ ligand. It had been avoided until now due to its obvious toxicity. The $AsPh_3$ ligand did indeed however offer a substantial improvement compared to entry 1, now giving diene **182** in 68% yield (entry 6). In order to improve on this still further, the reaction was performed as for entry 6 but with added $ZnCl_2$ (entry 7). This, however, had a deleteous effect on the reaction giving diene **182** in only 17%. Comparison of entries 1, 6 and 7 suggested to us that the catalyst derived from using the $AsPh_3$ ligand did not seem to tolerate the addition of $ZnCl_2$, but that the catalyst derived from P(2-furyl)$_3$ did. This seemed reasonable to us since Farina had reported that although a 1:2 ratio of Pd:$AsPh_3$ resulted in a more reactive catalyst than a 1:4 ratio, the former was considerably less stable.[67] However, the P(2-furyl)$_3$ ligand when used in a 1:2 ratio does not suffer from such instability, indicating that the catalyst derived from $AsPh_3$ is inherently less stable than its P(2-furyl)$_3$ partner. For this reason it has been recommended to use 1:2 Pd:P(2-furyl)$_3$ and 1:4 Pd:$AsPh_3$ stoichiometry.

The subsequent reaction employed addition of co-catalytic CuI (entry 8). However, it must be said that at the time we were investigating this reaction, there was little understanding as to the mechanistic basis for the copper effect. Therefore, we were surprised to find that in our hands, addition of co-catalytic amounts of CuI to the same reaction conditions employed for entry 6 failed to increase the rate or yield of reaction. On the contrary, it seemed to retard the coupling and gave a lower yield (entry 8 *vs* 6). This observation was at first surprising. Since then, however, much insight has been gained into the mechanistic basis for the "copper effect" mainly due to the thorough work of Farina. Since it is now understood that the rate enhancement due to the copper effect is essentially

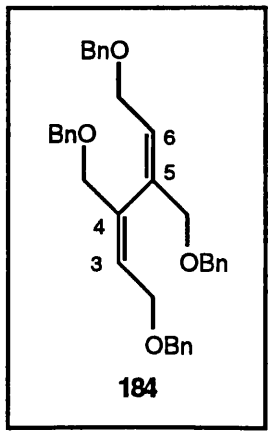
ineffective with the P(2-furyl)$_3$ and AsPh$_3$ ligands, this could be a possible explanation. However, the reaction was carried out in NMP, and since it is thought that there is a Sn/Cu transmetallation to yield an organocopper species (as discussed earlier), addition of CuI could have been beneficial. Presumably the observed negative effect is due in part to decreased catalyst stability under those conditions.

It was found that when the initial experiment with the P(2-furyl)$_3$ ligand (entry 1) was repeated under the same conditions but heated for longer periods of time (entries 9 and 10) increased yields were consistently obtained. The conditions of entry 10 now afforded the diene **182** in 86% yield. The final fine-tuning of the reaction conditions now simply required optimising the yield of coupled product in a shorter period of time. This was realised by increasing the reaction temperature enough to increase the rate of reaction whilst still suppressing the protodestannylation side reaction which would occur at still higher temperatures. Thus when performed at 65°C under the conditions of entry 6, the reaction proceeded in the same high yield, but now just required 16h for completion (entry 11).

This series of experiments highlighted the factors necessary for good yields of product, and with this reaction now proceeding in reproducibly high yield, attention was focused on the incorporation of the C3-, C4-, C5-, and C6- stereocentres in the asymmetric *cis* dihydroxylation of **182**. However, before this could be investigated it was thought prudent to perform an experiment which would check for scrambling at one of the alkenes to confirm the geometry of the 1,3-diene. It was thought that if the C5-C6 olefin had been scrambled, then reduction of the ester and benzylation would afford the symmetrical diene **183**, and conversely scrambling of the C3-C4 olefin would result in the symmetrical diene **184**.

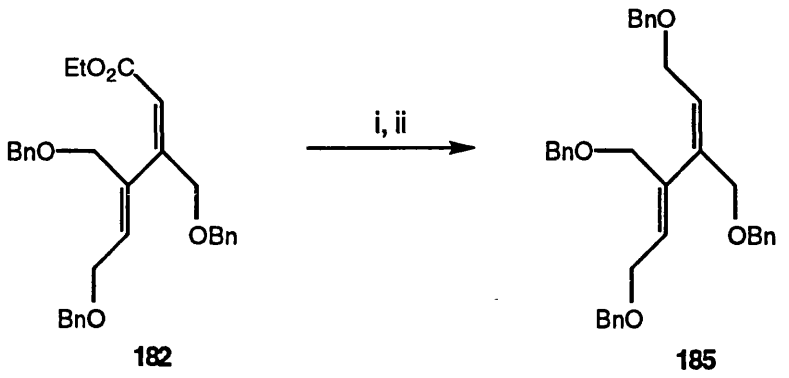


183



184

Thus, the dienic ester **182** was reduced to the corresponding dienic alcohol with DIBAL-H in 94% yield. Subsequent benzylation with BnBr / NaH in DMF quantitatively gave the tetrabenzyl diene **185** (Scheme 72).



Scheme 72

Reagents and conditions: i) DIBAL-H, CH_2Cl_2, -30°C, 93%; ii) BnBr, NaH, DMF, RT, 100%.

The ^1H NMR of **185** showed two alkenic signals, and the ^{13}C NMR was consistent with an unsymmetrical diene. We were therefore confident that the olefin geometries of the vinyl iodide and/or the vinyl stannane had been retained in the cross-coupling, though this would obviously not confirm whether both olefins had been scrambled at once, as that would also result in an unsymmetrical diene. However, this was thought to be unlikely, as it would mean that both double bonds would have to be completely isomerised. We were therefore confident that the geometry of both olefin coupling partners had been retained in the cross-coupling.

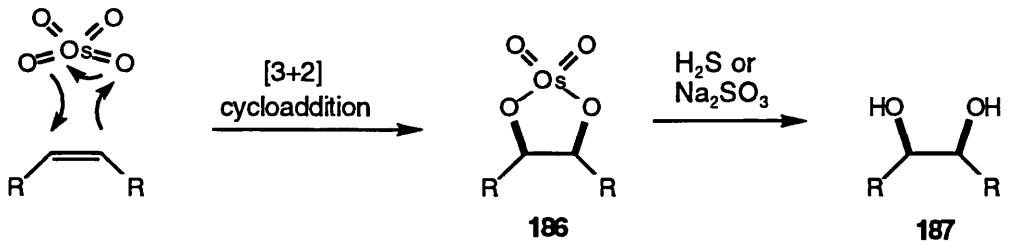
2.5 Incorporation of the stereocentres from C3 to C6 *via* Double Sharpless Asymmetric *cis*-dihydroxylation (AD).

In the following section, incorporation of the four contiguous stereocentres from C3 to C6 using Sharpless AD chemistry will be described. This reaction is the key point of our synthesis, and hence it is useful to give a brief historical introduction to the dihydroxylation reaction, followed by the development of the Sharpless AD reaction and some recent applications.

2.5.1 Stoichiometric *cis*-dihydroxylations

The first *cis*-dihydroxylation of olefins was first reported by Makowaka in 1908.[75] The original dihydroxylations required stoichiometric amounts of the expensive, volatile and highly toxic osmium tetroxide. Despite the unfriendliness of OsO_4, its specificity to react exclusively with double bonds was soon recognised as its major attribute. Not only that, but OsO_4 was found to react with virtually *all* double bonds, and had no particular substrate requirements.

The stoichiometric dihydroxylation was believed to proceed *via* a [3+2] cycloaddition reaction between OsO_4 and the olefin to give an osmate (VI) glycolate ester **186** (Scheme 73).



Scheme 73

The glycolate ester **186** is stable enough to be isolated and characterised. Subsequent reduction with H_2S or Na_2SO_3 affords the diol **187**. However, an alternative mechanistic proposal by Sharpless will be discussed later.

2.5.2 Catalytic *cis*-dihydroxylations.

Although the stoichiometric dihydroxylation of olefins is a reliable reaction, its application had remained minimal due to the expense incurred, not to mention the toxicity of OsO_4. Needless to say, catalytic variants of the reaction which have employed relatively inexpensive reagents for the re-oxidation of the Os(VI) have been vigorously pursued.

Inorganic co-oxidants such as the Hofmann reagent[76] (OsO_4-$NaClO_3$/$KClO_3$) or Milas's reagent[77] (OsO_4-H_2O_2) were among the first to be introduced, but over-oxidation of

the substrate was frequently a problem, which resulted in lower yields. Sharpless made significant improvements in the catalytic process by employing alkaline *tert*-butyl hydroperoxide (TBHP) as co-oxidant[78] which minimised over-oxidation, but the major breakthrough came from workers at Upjohn during the synthesis of a prostaglandin. The Upjohn process, as it is now commonly referred to, uses *N*-methyl-morpholine-*N*-oxide (NMO) as the stoichiometric co-oxidant[79] and requires only small (0.2-1%) amounts of OsO_4 in a one-phase acetone-water mixture. Under these conditions over-oxidation is almost completely suppressed, and the yields are frequently quantitative. These now experimentally simpler conditions have found widespread use in many natural product syntheses.

More recently, Yamamoto demonstrated that use of $K_3Fe(CN)_6$ as co-oxidant[80] in the presence of K_2CO_3 provided an excellent system for rendering the dihydroxylation process catalytic in OsO_4. This reagent combination will be returned to later since it has played a pivotal role in the development of the Sharpless AD (*vide infra*).

2.5.3 Asymmetric *cis*-dihydroxylation (AD).

Criegee's notable discovery of a dramatic rate enhancement in the osmylation reaction of alkenes by amines laid the foundation for the AD reaction. Criegee observed that addition of amines such as pyridine to the dihydroxylation reaction significantly increased its rate through formation of an electron-rich coordination complex with the osmium atom.[81] In addition, the first catalytic AD was reported by Kokubu and co-workers using Bovine Serum Albumin (BSA)-2-phenylpropane-1, 2-diolatodioxo-osmium (VI) complex.[82] It was proven that osmium tetroxide was bound to BSA through the amine residue (Figure 7). α-Methylstyrene gave its product diol with a 68% *ee* (S-configuration) using ^tBuOOH as co-oxidant (Scheme 74).

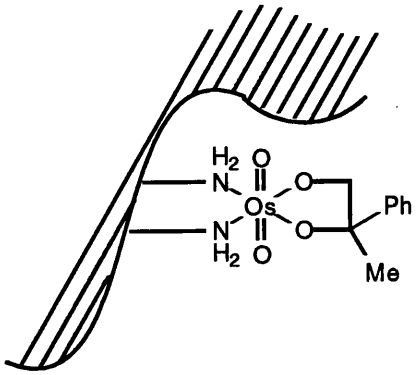
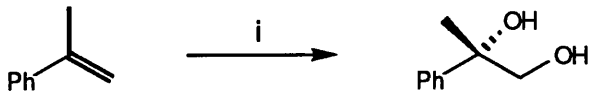


Figure 7: (BSA)-2-phenylpropane-1, 2-diolatodioxo-osmium (VI) complex

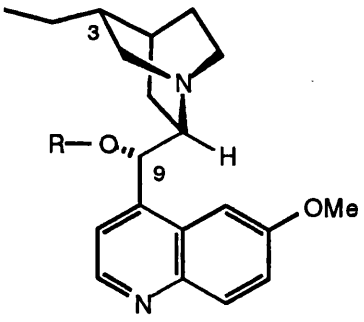


Scheme 74

Reagents and conditions: i) BSA, OsO_4, ^tBuOOH, pH 11 carbonate buffer, 25°C, 8h.

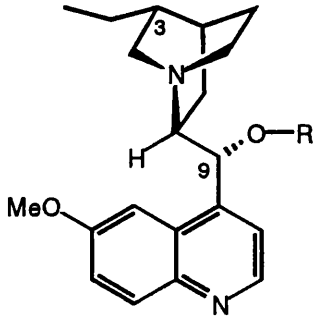
It is not surprising, then, that initial attempts at non-enzymatic asymmetric dihydroxylation by Sharpless and Hentges utilised chiral, enantiomerically pure pyridine derivatives.[83] However, the enantiomeric excesses of the product diols were poor due to the low affinity of these ligands for OsO_4. Griffith[84] had shown that quinuclidine had a much higher affinity for OsO_4 than pyridines, and hence Sharpless investigated chiral quinuclidines derived from the naturally occuring cinchona alkaloid family.[83]

The first ligands of this series were the acetate and then the chlorobenzoate (CLB) esters of dihydroquinidine (DHQD) **188** and dihydroquinine (DHQ) **189**, as depicted in Figure 8. Note that the DHQD and DHQ derivatives are diastereomers and not enantiomers since the C3 is the same configuration in both. They are often referred to as being *pseudo*-enantiomeric since they lead to diols of opposite configuration which have very similar enantiomeric excesses.



Dihydroquinidine (DHQD) derivatives

188 R=H, DHQD
R=Ac, (DHQD)-Ac
R=*p*-chlorobenzoate, (DHQD)-CLB



Dihydroquinine (DHQ) derivatives

189 R=H, DHQ
R=Ac, (DHQ)-Ac
R=*p*-chlorobenzoate,(DHQ)-CLB

Figure 8

Sharpless's assumption proved correct as these DHQD and DHQ derivatives afforded diols with moderate to good enantioselectivities. Initially these ligands were used stoichiometrically, but they were later used in catalytic amounts (*vide infra*).

Other workers in the AD area have investigated the use of chiral C_2-symmetric diamine ligands. Narasaka[85] was the first to report the use of these diamine ligands in 1986, and other groups also had considerable success as in most cases the reactions proceeded with up to 99% *e e* (Figure 9). Although the bidentate ligands generally gave superior enantioselectivity to the cinchona alkaloid ligands, they formed very stable chelate complexes with the osmium (VI) glycolate products which inhibited the hydrolysis and prevented *in situ* recycling of the osmium and ligand. Thus, AD reactions using these bidentate ligands are stoichiometric in both OsO_4 and chiral ligand.

There have been very few reports of other catalytic AD systems. Hirama recently reported that use of a monodentate DABCO derivative[90] (Figure 10) effected the AD under catalytic conditions, but the enantiomeric excesses were only moderate. Murahashi and co-workers[91] enjoyed greater success when they utilised chiral isoxazolidines to effect the catalytic AD, giving diols in up to 73% *ee* (Figure 10).

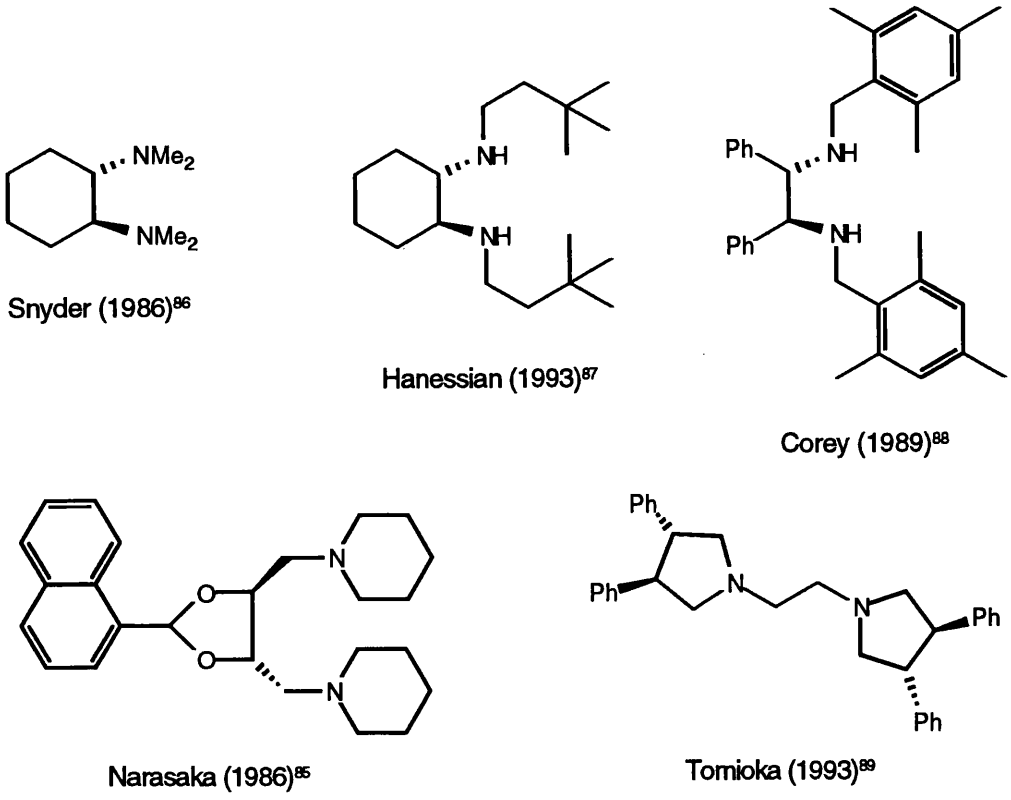


Figure 9: Chiral diamine ligands for *Stoichiometric* AD

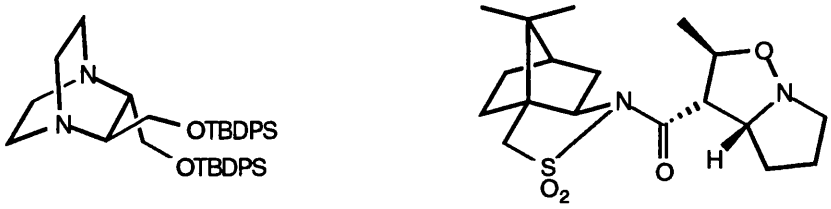
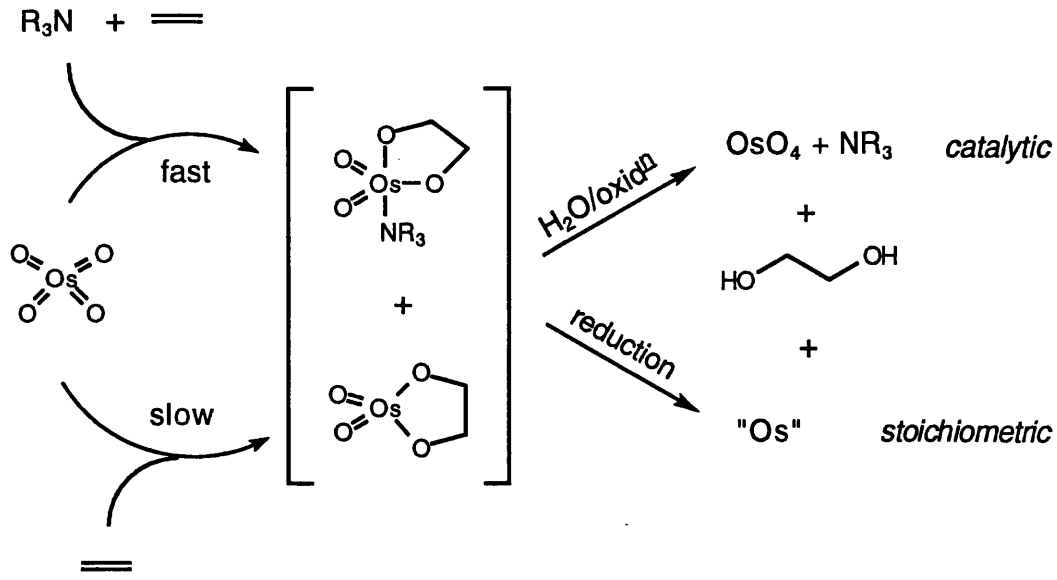


Figure 10: Recent monodentate ligands for *catalytic* AD

Sharpless realised that the success of the catalytic AD would rely on the reaction being funnelled through a pathway involving the chiral catalyst, and introduced the concept of ligand accelerated catalysis.[46] The principle of the ligand acceleration effect (LAE) for the AD reaction is illustrated in Scheme 75.

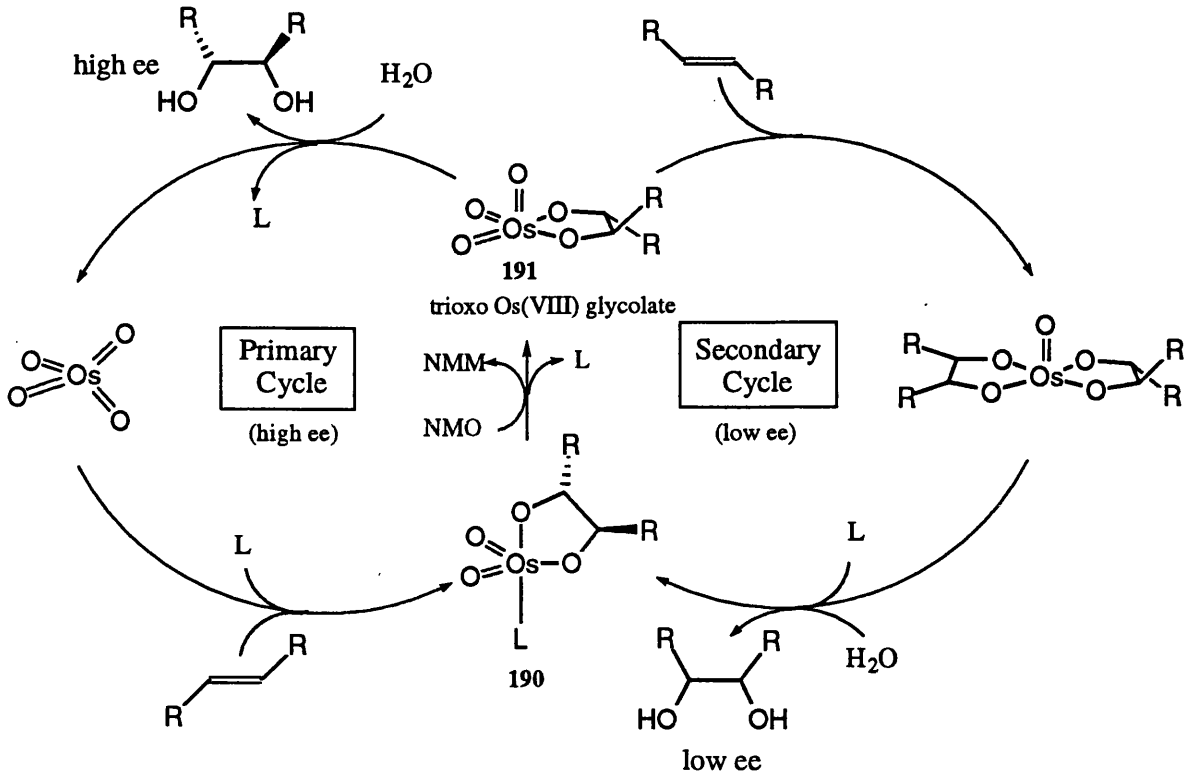


$$LAE = \frac{\text{Saturation Rate with Ligand}}{\text{Rate without Ligand}}$$

Scheme 75

If a chiral ligand can activate a catalyst such that it is only significantly active when bound as a catalyst-ligand complex, then asymmetric induction will be maximised. For the AD reaction, the original pyridine ligands had too low an affinity for OsO_4 and hence the LAE was low, giving rise to low asymmetric induction. The bidentate ligands formed a catalyst-ligand complex that was so tight that although it accelerated the reaction and hence maximised the LAE, it was unable to dissociate at the Os(VI) glycolate stage and hence unable to re-enter the catalytic cycle. The cinchona alkaloid ligands are a compromise between maximising both the LAE and catalytic turnover. They form a catalyst-ligand complex that is tight enough to accelerate the reaction, but not so tight that it would slow down subsequent steps in the catalytic cycle, and hence they provide greater turnover.

Sharpless combined the cinchona alkaloid stoichiometric dihydroxylation process with the Upjohn NMO procedure and in 1988 reported the first non-enzymatic catalytic AD.[92] However, the enantiomeric excesses of the resulting diols obtained under the catalytic procedures were initially lower than those obtained in the stoichiometric reaction. The reason for this decrease in ee was found to be due to the presence of a secondary catalytic cycle[46] in which the chiral ligand did not participate, hence lowering the ee (Scheme 76).

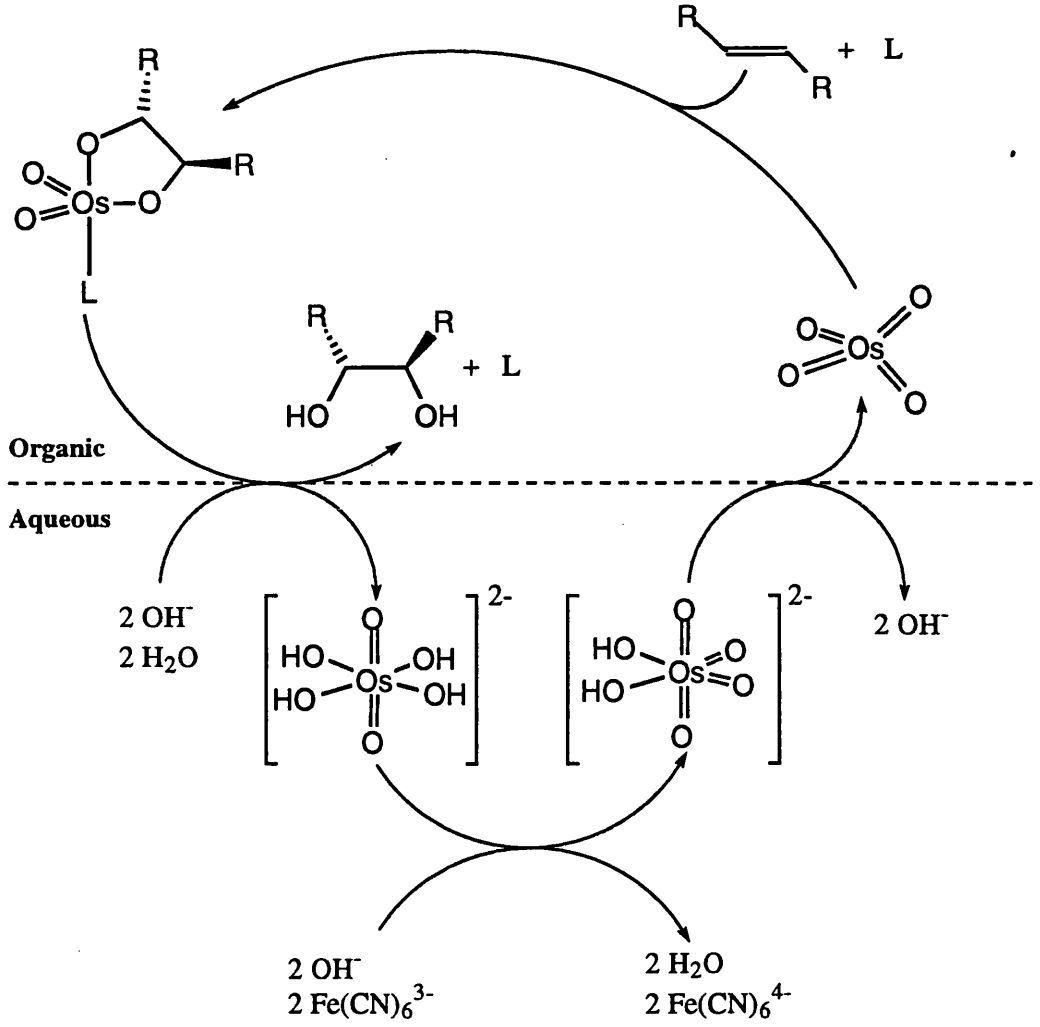


Scheme 76: Two catalytic cycles exclusive to the NMO system

It was suggested that the initially formed Os(VI) monoglycolate species **190** was oxidised by the NMO to the trioxo Os(VIII) glycolate **191**. This Os(VIII) glycolate species is able to perform a further dihydroxylation, but it now lacks a coordination site for the chiral ligand L, and so this dihydroxylation takes place with only low or no enantioselectivity. This results in diols with reduced ee's.

A partial remedy to this problem was slow addition of the alkene, thereby allowing hydrolysis of the Os(VI) monoglycolate species **190** before the NMO had a chance to oxidise it to the trioxo Os(VIII) glycolate **191**.

Sharpless has since made dramatic improvements in the AD reaction. This has been due mainly to three key discoveries in his group. It was found that use of $K_3Fe(CN)_6$ instead of NMO as the stoichiometric re-oxidant under two-phase conditions virtually eliminated the participation of the undesired second catalytic cycle (Scheme 77).

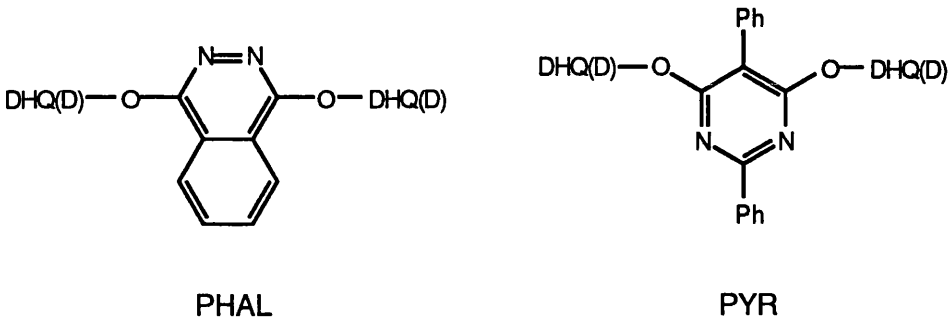


Scheme 77:Catalytic cycle under the two-phase $K_3Fe(CN)_6$ system

Under these conditions, the only oxidant in the organic layer, which is where the dihydroxylation occurs, is OsO_4, . The co-oxidant $K_3Fe(CN)_6$ is now confined to the aqueous layer (unlike the NMO case). The resulting Os(VI) monoglycolate ester undergoes hydrolysis to give diol and ligand in the organic layer and Os(VI) must return to the aqueous layer before its re-oxidation can occur, thereby preventing entry of Os(VI) glycolate into the second cycle.

The second key discovery was the so called "sulfonamide effect". It was found that addition of methanesulfonamide considerably accelerated the hydrolysis of the Os(VI) glycolate product, and the reaction times were greatly reduced. This allowed high catalytic turnover even with sterically hindered olefins and greatly increased the scope of the reaction. It also permitted the reaction to be run at 0°C which normally has a beneficial effect on the stereoselectivity.

The third and very important discovery came about as a result of wide screening of over 250 different cinchona alkaloid derivatives for the AD process. A new second generation of C_2-symmetric dimeric ligands employing a phthalazine (PHAL) or diphenylpyrimidine (PYR) core emerged. These new ligands were found to greatly outperform the first generation monomeric ligands in both the enantioselectivity and scope of the reaction (Figure 11).



PHAL PYR

Figure 11: Second generation C_2-symmetric Sharpless AD ligands

It was also found that dipotassium osmate dihydrate ($K_2OsO_4 \cdot 2H_2O$) was a suitable non-volatile replacement for OsO_4, and this allowed for the formulation of a premix containing all the required reagents, including the ligand. These AD-mixes are now commercially available from Aldrich under the names AD-mix-α or AD-mix-β, depending on whether the $(DHQ)_2$-PHAL or $(DHQD)_2$-PHAL ligands are present, respectively. They contain 0.2 mol% $K_2OsO_4 \cdot 2H_2O$, 1 mol% ligand, 300 mol% K_2CO_3 and 300 mol% $K_3Fe(CN)_6$.

Through a combination of models of the reaction and knowledge of the absolute configuration of the diol products and consideration of a vast amount of experimental data, an empirical mnemonic device has been proposed for predicting the enantiofacial selectivity in the reaction (Figure 12). Use of the device involves placement of the olefin in the plane such that the smallest substituent (usually a hydrogen) is in the southeast quadrant. This takes precedent over all else since this is by far the major steric barrier. An olefin positioned according to this and the other quadrant constraints will be attacked from the top, β-face with DHQD derivatives. Conversely, use of DHQ derivatives results in attack from the bottom, α-face.

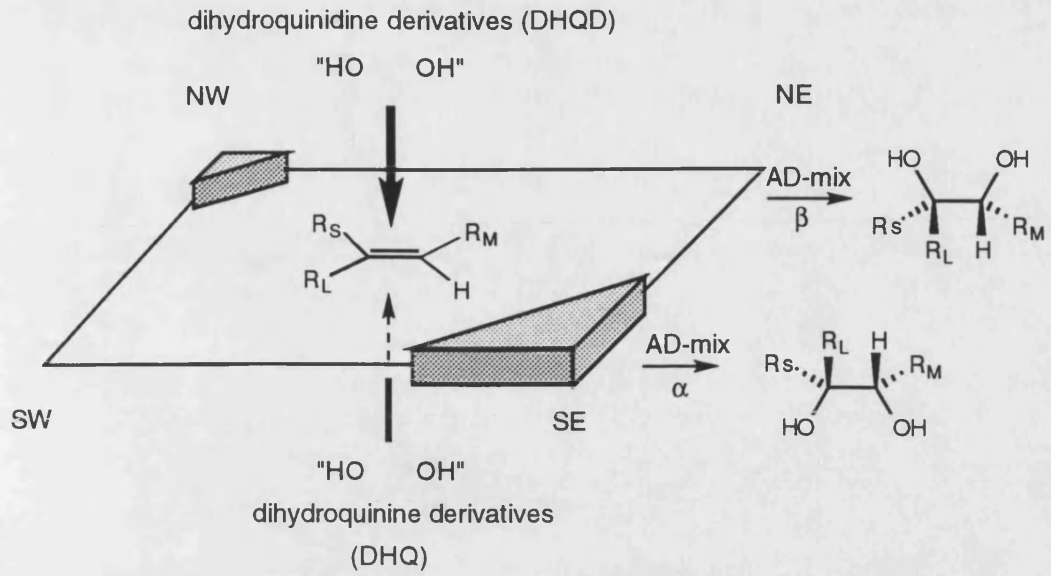
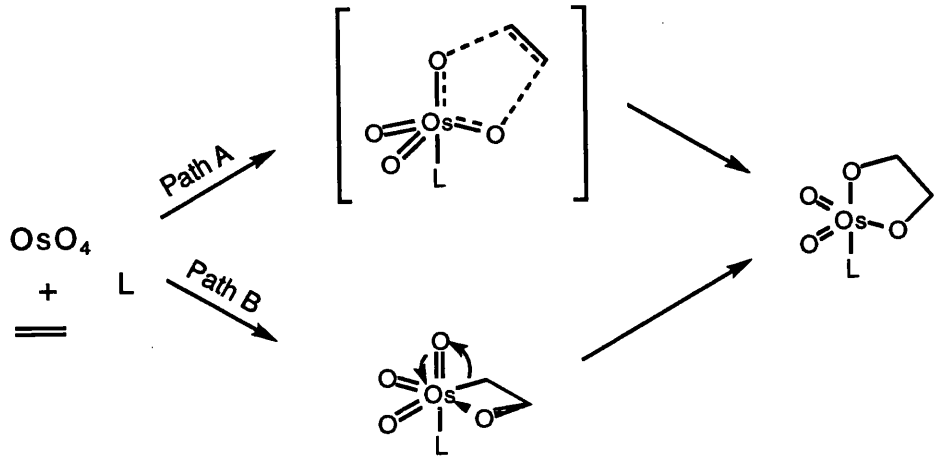


Figure 12: Empirical mnemonic device for predicting face selectivity

The southeast quadrant, and to a much lesser extent the northwest quadrant of this device present steric barriers, whereas the northeast quadrant has been regarded as sterically neutral.The southwest quadrant is regarded as being an attractive area, especially suited for flat aromatic substituents.

The precise mechanism and origin of the enantioselectivity of the AD has been the focus of extensive investigation. Criegee originally proposed a concerted [3+2] cycloaddition of OsO_4 with an olefin to give directly the Os(VI) glycolate (path A) (Scheme 78), which is then hydrolysed either as part of a catalytic cycle or stoichiometrically, to give the corresponding diol. However, in 1977 Sharpless suggested a stepwise reaction which is initiated by a [2+2]-like addition of the olefin across an Os=O bond (path B), followed by rearrangement of the resulting osmaoxetane intermediate to the glycolate product.[46] To date no definite conclusions have been made but Sharpless's recent observations of a non-linear Eyring relationship between *ee* and temperature is inconsistent with Criegee's *one-step* [3+2] mechanism. These new data, in combination with high level *ab initio* calculations that showed osmaoxetanes to be energetically accessible minima on the potential energy surface, suggest that the osmaoxetane pathway may be in operation.



Scheme 78

However, Corey has obtained conflicting kinetic data to provide evidence for the [3+2] cycloaddition.[93] The precise mechanism is clearly still a long way from being fully understood.

Sharpless has also probed the nature of the ligand and gained valuable insight as to the origin of the enantioselectivity in the AD reaction. The most striking finding was the discovery of an enzyme-like binding pocket present in the dimeric cinchona alkaloid ligands such as the phthalazine class. Figure 13 highlights the relationship between ligand structure, binding and ceiling rate constants. The rates and enantioselectivities are considerably influenced by the nature of the O-9 substituent, though little effect is observed in the binding of the ligand to OsO_4 if changes are made here.

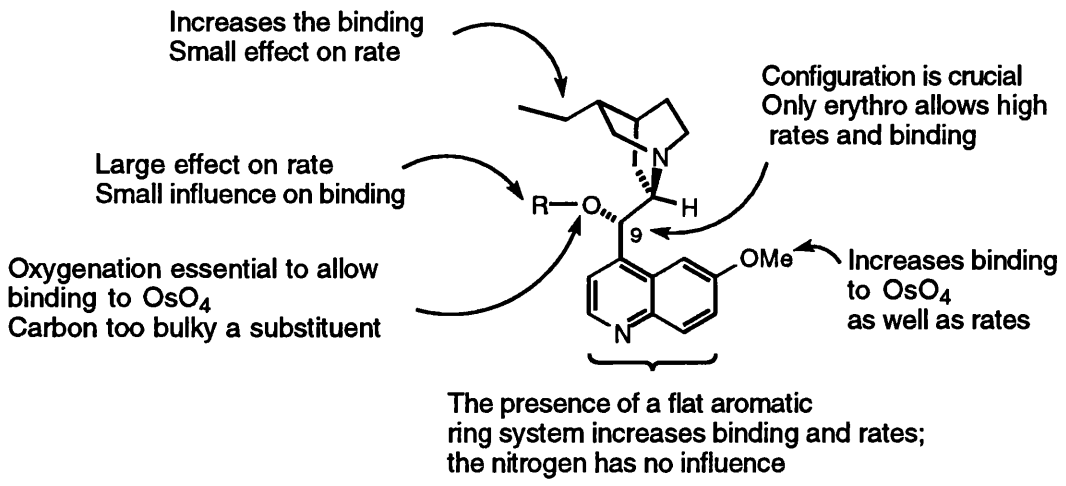


Figure 13

It is thought that the AD's face selectivity is chiefly governed by two major factors. The first is believed to be due to stabilising stacking interactions between one of the substituents on the osmaoxetane (the olefin substituent from the SW quadrant) and the C9 OR substituent of the ligand. The second factor arises from destabilising repulsive interactions between the smallest substituent of the osmaoxetane (the smallest substituent of the olefin) and H9 of the ligand (Figure 14).

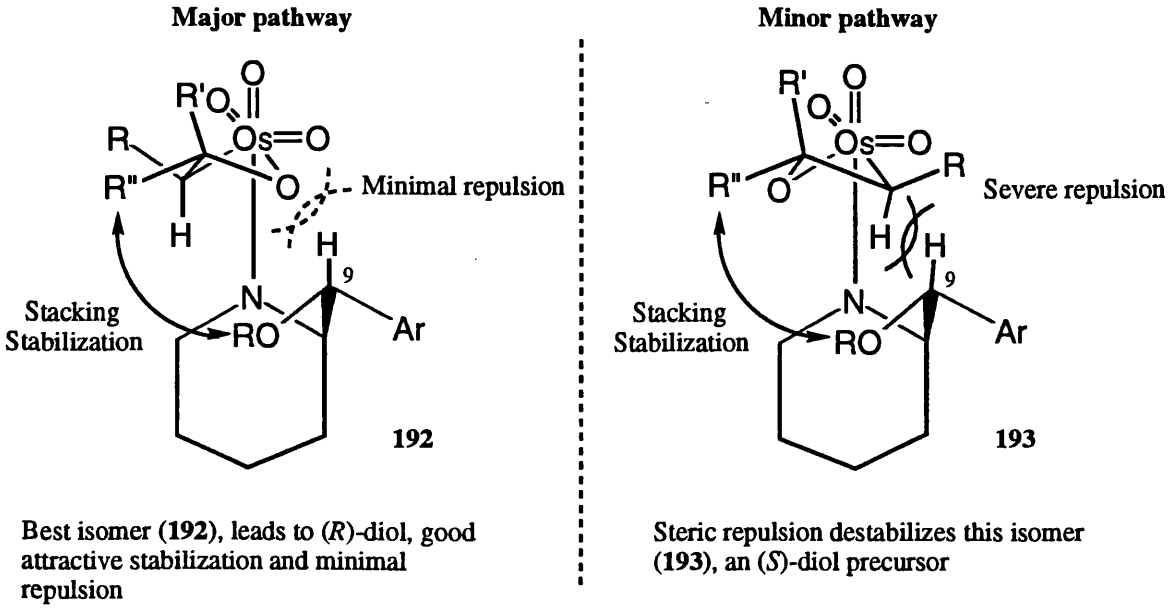
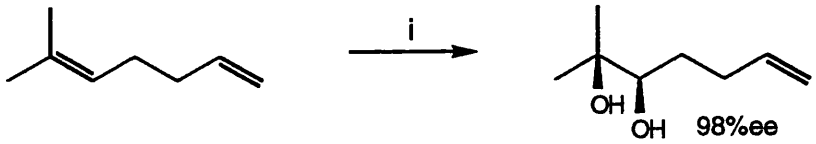


Figure 14: The interplay of two crucial interactions, one attractive, the other repulsive, provides a simple rationale for the face selectivity in the AD reaction.

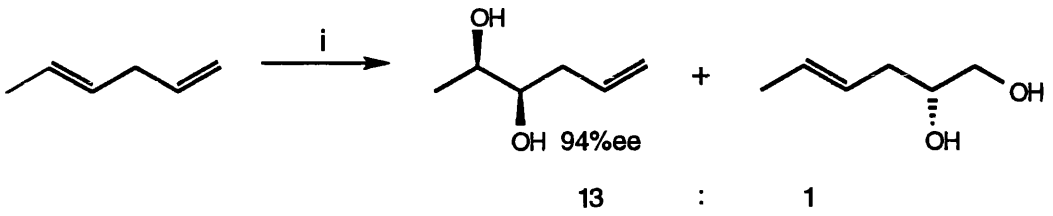
2.5.4 The AD of poly-unsaturated substrates

As well as substrates containing a single olefin, polyenes can also serve as substrates for the AD. Mono-dihydroxylation can be achieved for polyenes with either isolated or conjugated double bonds using the two-phase ferricyanide system.[94] The regioselectivity of mono-dihydroxylation of a polyene will be determined by both steric and electronic effects. The osmylation of isolated double bonds will occur preferentially at the more electron rich double bond. It has been shown that dihydroxylation of *trans*-1,2-disubstituted and trisubstituted olefins proceeds much more readily than with *cis*-1,2-disubstituted and terminal alkenes (Schemes 79 and 80).[94]



Scheme 79

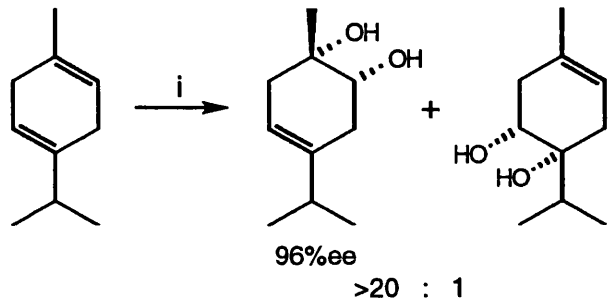
Reagents and conditions: i) AD-mix-β, ^{t}BuOH/H_2O, 0°C, 73%.



Scheme 80

Reagents and conditions: i) AD-mix-β, ^{t}BuOH/H_2O, 0°C, 56%.

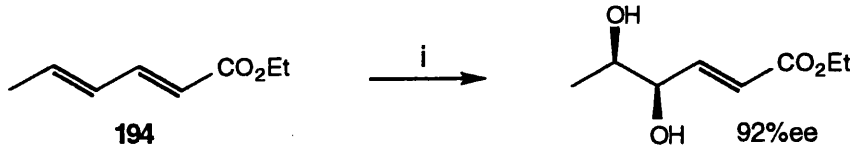
For isolated olefins with electronically very similar double bonds, the sterically less hindered site is dihydroxylated preferentially (Scheme 81).[46]



Scheme 81

Reagents and conditions: i) AD-mix-β, ^{t}BuOH/H_2O, 0°C, 84%.

Conjugated polyenes can also be preferentially mono-dihydroxylated under the two-phase ferricyanide system.[94] The resulting ene-diol is in most cases unable to undergo a further dihydroxylation due to the inductively deactivating effect the hydroxyls have on the remaining olefin(s). The regioselectivity will again be governed by steric and electronic effects. For example, the dienic ester **194** is selectively dihydroxylated at the more electron rich olefin furthest from the electron withdrawing ester (Scheme 82).[94]

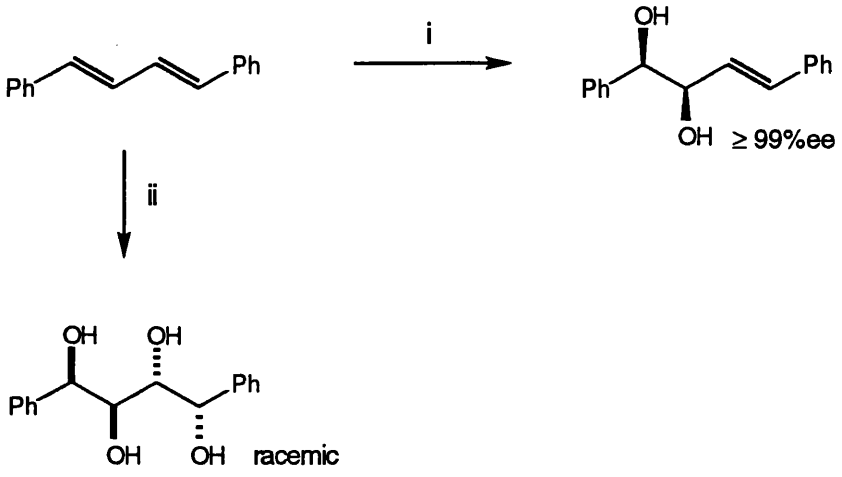


194

Scheme 82

Reagents and conditions: i) AD-mix-β, $MeSO_2NH_2$, $^tBuOH/H_2O$, 0°C, 78%.

Sharpless has demonstrated that exhaustive dihydroxlation of conjugated dienes with OsO_4 in the presence of NMO in the one-phase system can be achieved, affording polyols.[95] This is in stark contrast to the two-phase ferricyanide AD process which stops at the ene-diol stage (Scheme 83).



Scheme 83

Reagents and conditions: i) AD-mix-β, $MeSO_2NH_2$, $^tBuOH/H_2O$, 0°C, 84%; ii) OsO_4, NMO, acetone/water, RT.

The poly-dihydroxylation in the NMO reaction is thought to result from the participation of the second catalytic cycle oxidant, the trioxo Os(VIII) glycolate **191** (Scheme 76). It was established that 1,2-dihydroxy-3-enes were uniquely reactive toward further oxidation in the one-phase NMO system. The current hypothesis is that the trioxo Os(VIII) glycolate **191** can attain favourable hydrogen bonding interactions in the transition state between its oxo ligands and the ene-diol hydroxyls. This hypothesis of stabilising hydrogen bonding interactions accounts for the rate enhancement observed for the ene-diols as protection of the two hydroxyl groups of the ene-diol results in a considerable decrease in rate. In addition to this, there is a decidely marked tendency for each new subsequent

dihydroxylation to occur adjacent to the previous site of attack and from the opposite face, leading to polyols with a 1,2-*syn*-2,3-*anti*-3,4-*syn* arrangement down the chain. This is consistent with Kishi's empirical rule[96] which suggests that osmylation will occur *anti* to the previous oxygen functionality with the alkene in the conformation shown in Figure 15.

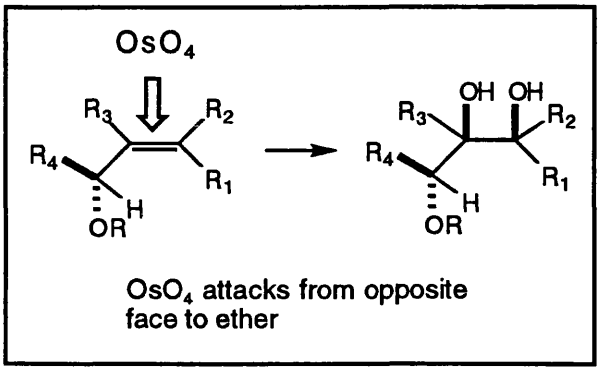
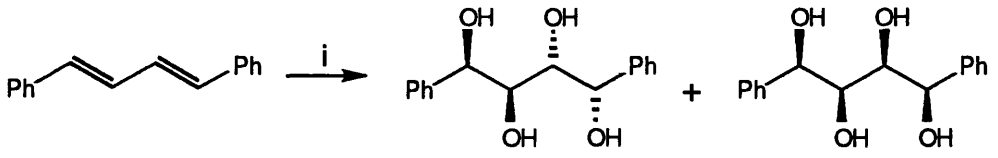


Figure 15: Kishi's empirical model

It is important to note that the intrinsic diastereofacial preference described in Scheme 83 mismatches the selectivity imposed on the system by the DHQD-CLB ligand. However, the induction by the ligand is too weak to overcome the strong *anti* diastereoselectivity exhibited by the trioxo Os(VIII) glycolate oxidant and merely results in reducing the ratio from 16:1 to 6:1 (Scheme 84).



No ligand present:	16	:	1
DHQD-CLB present:	6	:	1

Scheme 84

Reagents and conditions: i) OsO_4, NMO, acetone/water, RT.

2.6 Application of the AD to our 1,3-diene

If the Sharpless mnemonic is applied to our 1,3-diene **182** it can be seen that the same chiral ligand, a DHQD derivative, is required for osmylation of both double bonds (Scheme 85).

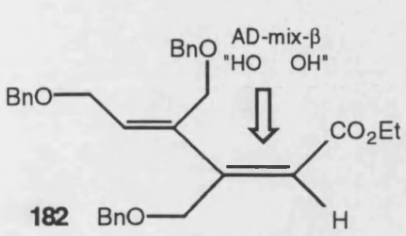
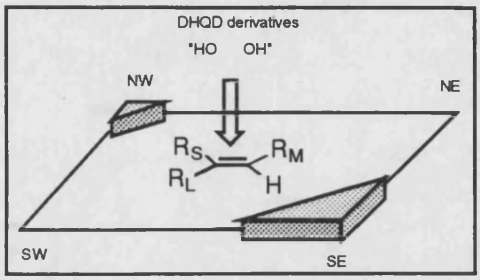


Figure 16



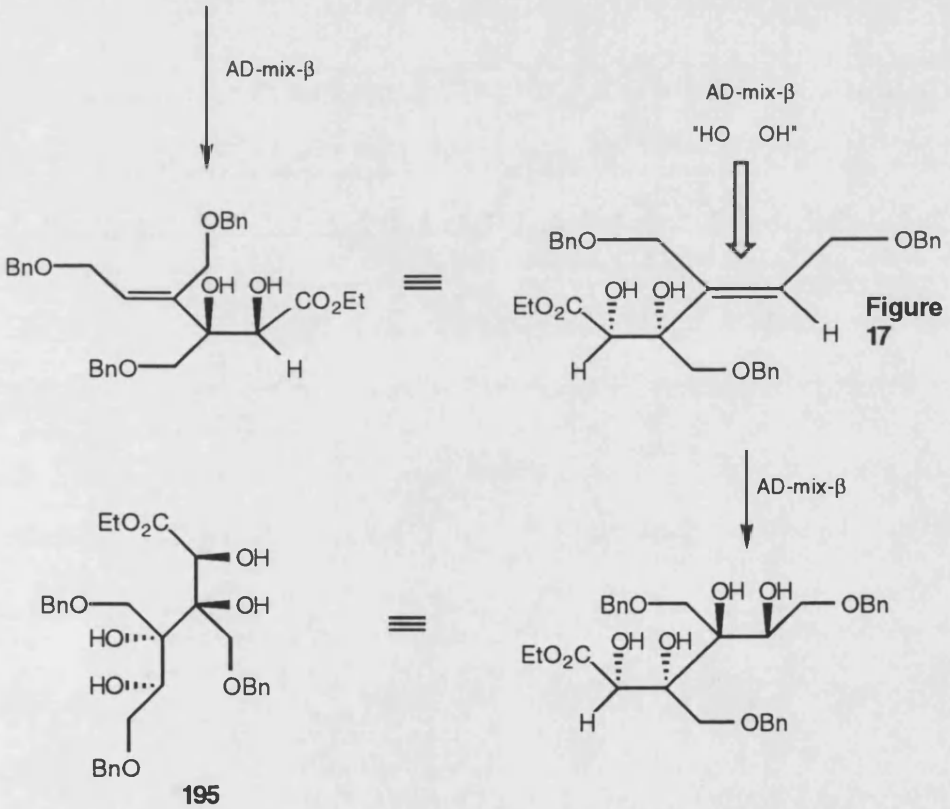


Figure 17

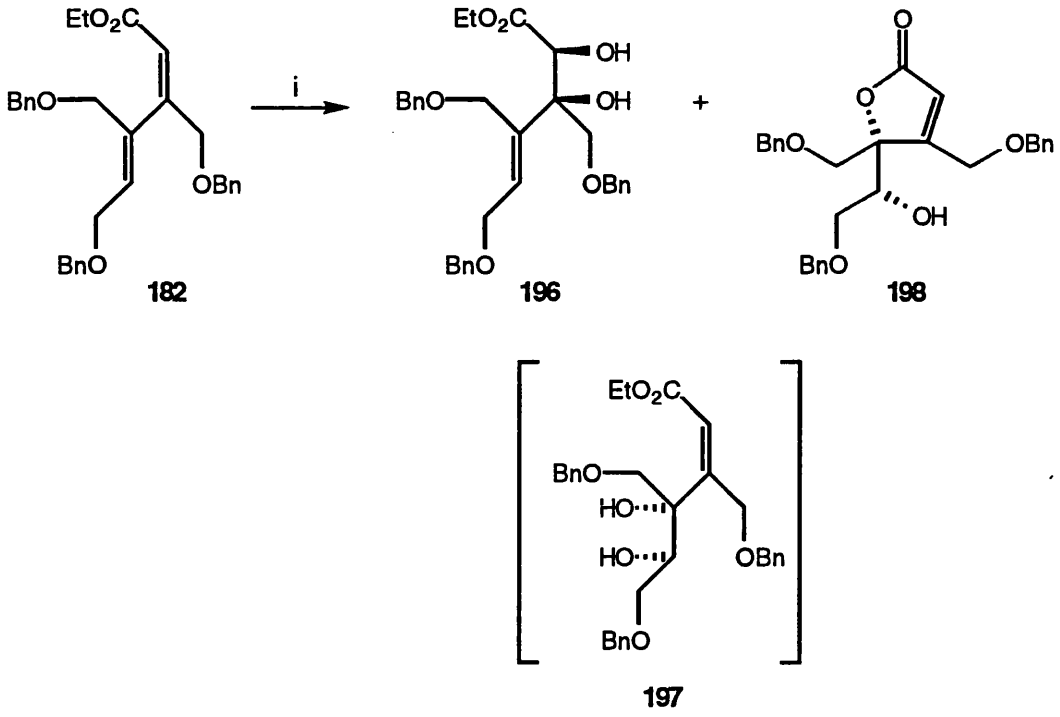
Scheme 85

Figure 16 shows that the only substituent mismatch is that the NW quadrant has the largest group, where the mnemonic requires the smallest group there (since the NE corner is sterically neutral, the R_M group is less important). Figure 17 shows we have a perfect match

with the mnemonic. We therefore hoped we could osmylate both double bonds at once to give predominantly one diastereomeric tetraol **195** with high enantiomeric purity.

When we initially examined this reaction, we were unaware that *exhaustive* dihydroxylation of conjugated dienes had been reported in the one-phase NMO system. However, although dihydroxylation of conjugated dienes had been reported in the two-phase ferricyanide system to stop at the ene-diol stage, in some cases it was possible to re-submit the resulting ene-diol to the same two-phase ferricyanide system and obtain the corresponding tetraol. The following results describe our attempts to dihydroxylate both double bonds at once in a one-pot procedure *under the two-phase $K_3Fe(CN)_6$ system.* We soon became aware, however, of the need to use the one-phase NMO system to dihydroxylate both double bonds at the same time.

The dienic ester **182** was subjected to the AD reaction. Treatment of **182** with AD-mix-β at 0°C in $^tBuOH:H_2O$ (1:1, v/v) with one equivalent of $MeSO_2NH_2$ gave no reaction after 3h. It had been reported that for alkenes which react sluggishly at 0°C, the AD could be performed at RT.[97] However, after 17h at RT, TLC still indicated mainly starting material, and so additional OsO_4 and ligand were added. The reaction was very slow, and after 5d still *ca.* 50% starting material was observed. Reductive workup with Na_2SO_3 afforded two products as an inseparable mixture in 38% yield. ^1H NMR analysis of this mixture indicated it was a 2:1 ratio of what was thought to be the two isomeric ene-diols **196** and **197**, the major component being **196** (Scheme 86). The regioisomers were distinguishable based on the ^1H NMR resonance for the olefinic proton in **197** being a singlet, hence allowing assignment as to which double bond had been osmylated.

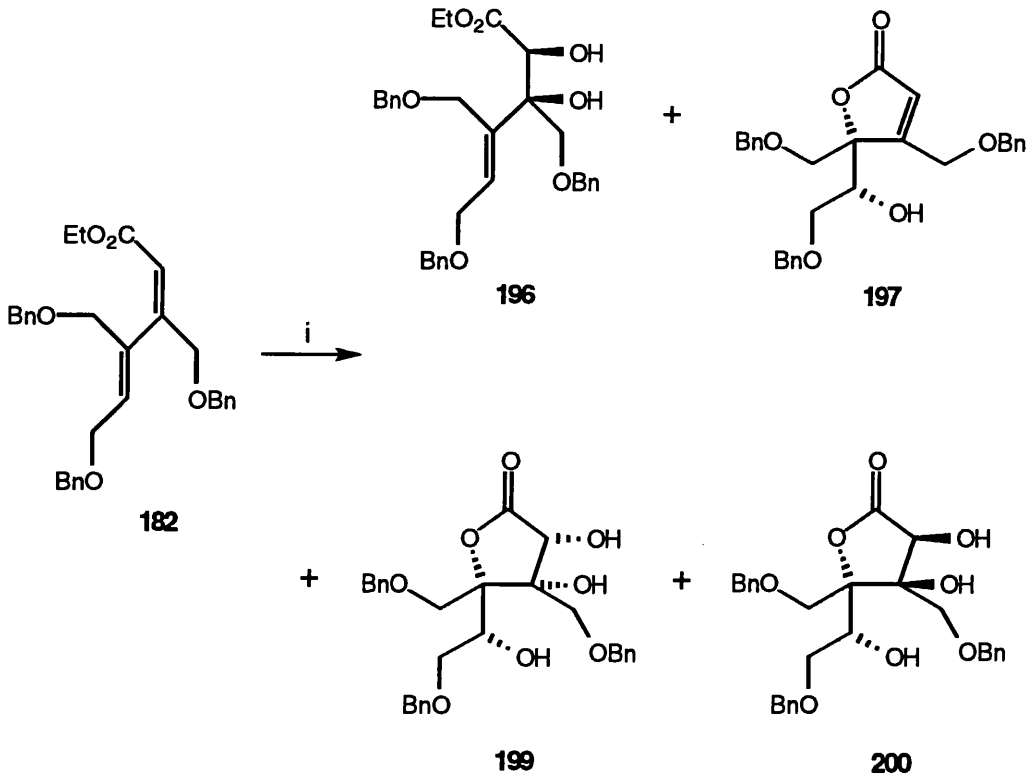


Scheme 86

Reagents and conditions: i) AD-mix-β, $^tBuOH/H_2O$, 1 eq $MeSO_2NH_2$, additional OsO_4 and $(DHQD)_2PHAL$, RT, 5d, 38%.

The next attempt employed AD-mix-β supplemented with 4 mol% $(DHQD)_2PHAL$ and 1 mol% OsO_4, running the reaction at RT. After 17h, TLC indicated mainly starting material, and after 6d it was necessary to add still more ligand and OsO_4. After 12d, the reaction was worked up. Although it had initially proved difficult to separate the two products, a solvent system was eventually found to achieve their separation effectively. The ^1H NMR of the first eluted compound showed the disappearance of the ester functionality and that the C3-C4 double bond had been dihydroxylated. It was thought that after dihydroxylation, the ene-diol **197** had lactonised. It was not known whether the five-(**198**) or six-membered butenolide had been formed. However, only the five-membered butenolide has an oxidisable secondary hydroxyl. Thus, the butenolide product was subjected to the Dess-Martin periodinane reagent.[98] This gave a new product, which from the ^1H and ^{13}C NMR suggested to us that benzylic oxidation had taken place but the structure is not conclusively known. However, from these limited data the butenolide is tentatively assigned to be **198**, which was isolated from the AD reaction in 8% yield. The second compound eluted was the diol **196**, isolated in 18% yield.

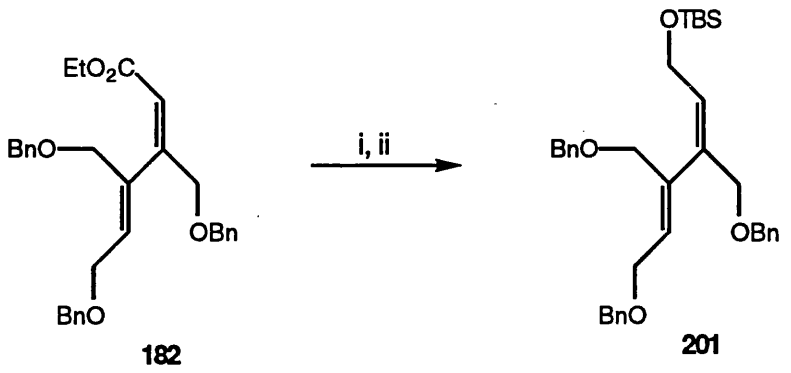
At that time it had very recently been reported by Bitmann and co-workers[99] that the use of $K_2S_2O_8$ as co-oxidant allowed the use of reduced volumes of solvent, and promoted the catalytic reaction. Since it was our aim to obtain the tetraol **195,** the diene **182** was submitted to the AD reaction, but five times more concentrated with 1 equivalent of $K_2S_2O_8$ as co-oxidant. We were delighted to find that after just 2h virtually all of the starting material had been consumed (TLC). However, even after 3d, TLC still did not indicate the presence of a more polar compound that could be tetraol. The beneficial rate enhancement on adding $K_2S_2O_8$ had been realised, however, and was used in all subsequent two-phase AD reactions. A series of experiments was run in order to try to obtain tetraol under forcing conditions. Use of several equivalents of both $K_2S_2O_8$ and $CH_3SO_2NH_2$, in conjunction with additional OsO_4 and ligand in concentrated reactions, led to very low yields of what appeared by ^1H NMR to be the two diastereomeric triols **199** and **200** as an inseparable mixture, arising from lactonisation, as well as the mono-dihydroxylated products **196** and **197** (Scheme 87).



Scheme 87

Reagents and conditions: i) AD-mix-β, $^tBuOH/H_2O$, 2 eq $MeSO_2NH_2$, 2 eq $K_2S_2O_8$, additional OsO_4 and $(DHQD)_2PHAL$, RT.

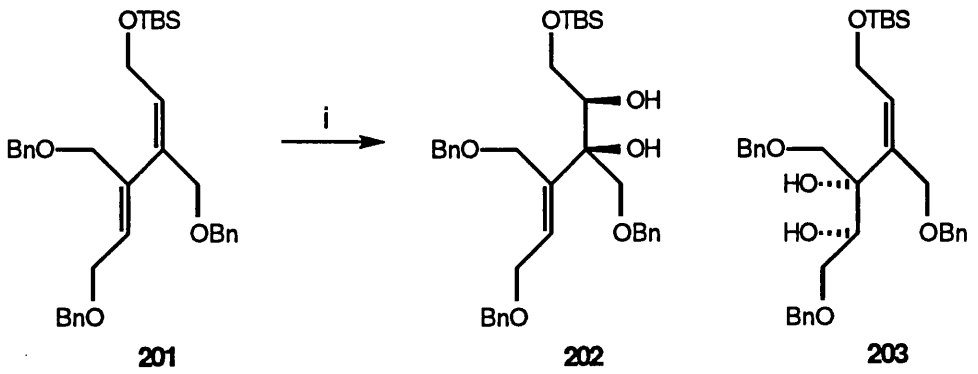
It was decided to reduce the ester functionality to a protected alcohol oxidation level since it was thought that its presence was a partial cause for the slow rate of reaction by making the olefins electron deficient. Reduction would also prevent the lactonisation which was complicating matters still further. To this end, reduction of the dienic ester **182** with DIBAL-H at -30°C followed by subsequent protection as the TBS ether afforded the diene **201** (Scheme 88).



Scheme 88

Reagents and conditions: i) DIBAL-H, CH_2Cl_2, -30°C, 93%; ii) TBSCl, imidazole, DMF, RT, 19h, 98%.

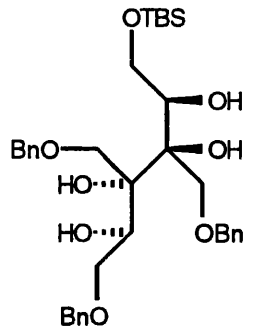
However, subjection of **201** to what we then regarded as our 'normal conditions' of using Super AD-mix (which we refer to as SAD-mix!), that is, AD-mix-β, two equivalents of $CH_3SO_2NH_2$, two equivalents of $K_2S_2O_8$ and a small supplement of both OsO_4 and ligand, run in the literature reported concentration,[97] resulted in very slow rates of reaction. No regioselectivity was observed, a mixture of diols **202** and **203** being obtained (Scheme 89).



Scheme 89

Reagents and conditions: i) AD-mix-β, $^tBuOH/H_2O$, 2 eq $MeSO_2NH_2$, 2 eq $K_2S_2O_8$, additional OsO_4 and $(DHQD)_2PHAL$, RT, 17%.

It was found that increasing the concentration greatly increased the rate of dihydroxylation, and under very forcing conditions (OsO_4 and ligand supplements in combination with several equivalents of both $CH_3SO_2NH_2$ and $K_2S_2O_8$ in considerably more concentrated reactions) complete starting material consumption was observed after typically 4h. Under these conditions the reactions rapidly led to a *ca.* 1:1 ratio of regioisomeric diols **202** and **203** (3-5h), but after many days, the desired tetraols were now observed. However, even after a week the desired tetraol **204** was only obtained in 8% yield.



204

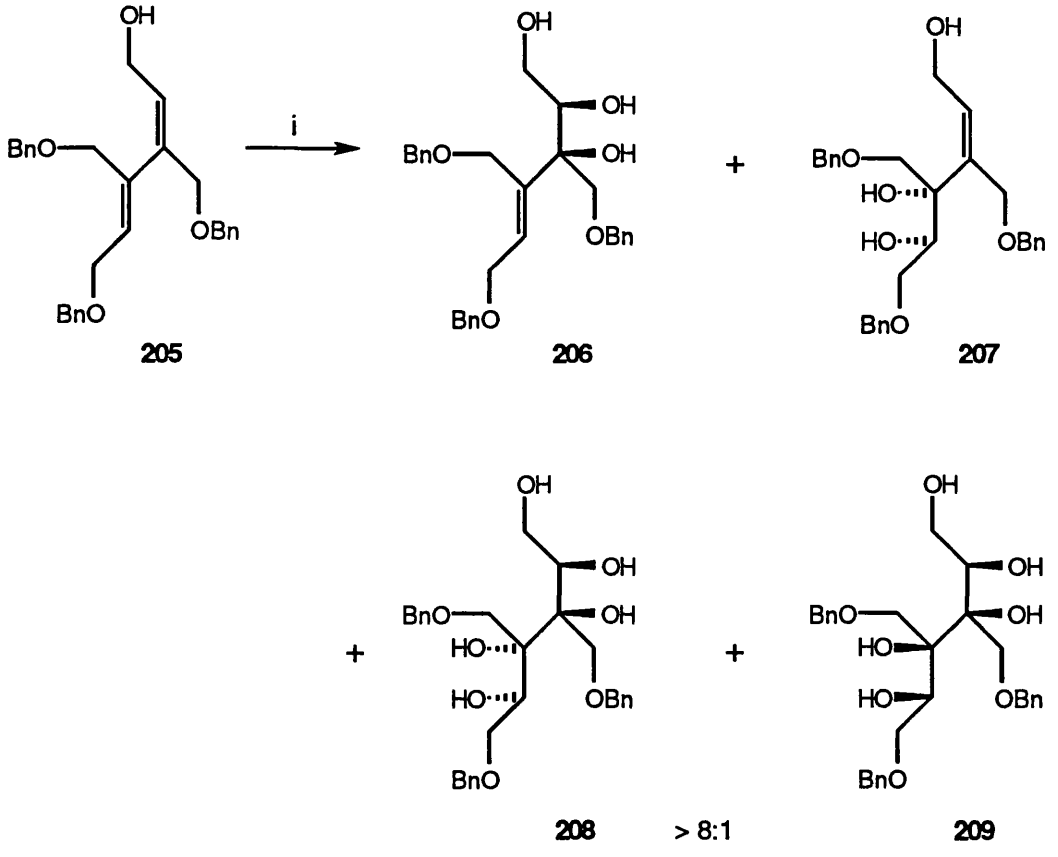
At that time it was thought that the environment was too sterically crowded for the large dimeric $(DHQD)_2PHAL$ ligand to operate in, and so it was thought advisable to try a change in ligand. The DHQD-CLB ligand was tried, since it is monomeric and smaller and it was known to still give good enantioselectivity for trisubstituted alkenes.[46]

The silyl ether **201** was thus submitted to our normal AD conditions using DHQD-CLB as ligand. After 1d there was *ca.* 50% starting material left, but very good regioselectivity was observed for one of the diols, as seen by the ^1H NMR ratio of *ca.* 10:1, though it was not possible to determine which of the two olefins had been dihydroxylated. After consumption of all the starting material, the crude ^1H NMR showed mainly one diol, but unfortunately very little tetraol, even when left for considerable amounts of time.

For the purpose of eventual selective oxidation of the C7 hydroxyl, we required to protect the tetraol **204** as the bis-acetonide. With the small amounts of tetraol **204** available at that time, we found that treatment of **204** with dimethoxypropane (DMP) and catalytic *p*-TsOH led to cleavage of the silyl ether.

The low rate in the AD reaction with the silyl protecting group, and its subsequent cleavage during the bis-acetonide formation, led us to invesigate the AD on the free hydroxyl compound **205**. To our delight, when the dienic alcohol **205** was submitted to our normal conditions, run at the literature reported concentration, virtually all starting material had been consumed within 16h. This was a much increased rate in reaction with respect to both the ester **182** and silyl protected derivative **201** which had both needed greatly increased reaction

concentrations. However, virtually no regioselectivity was observed, a *ca.* 1:1 mixture of triols **206** and **207** being obtained. The desired pentaol **208** remained elusive until the reaction was run at three times the concentration with an additional 10 mol% OsO_4 and 30 mol% ligand. These conditions yielded the pentaols **208** and **209** in 10% yield as an inseparable mixture (Scheme 90). However, what was encouraging was that the diastereomeric ratio of **208** to **209** appeared to be better than 8:1. The diastereomeric ratio was measured by integration of the peaks in the ^{13}C NMR spectrum of the crude mixture with the pulse delay having been set to 10 seconds. This enables meaningful integration of the carbon signals as full relaxation is achieved within that time period. All of our future diastereomeric ratios from AD reactions were measured in the same way.



Scheme 90

Reagents and conditions: i) AD-mix-β, $^tBuOH/H_2O$ (3x lit. concentration), 2 eq $MeSO_2NH_2$, 2 eq $K_2S_2O_8$, additional 10% OsO_4 and 30% $(DHQD)_2PHAL$, RT.

No mention has been made yet as to the enantioselectivity of these reactions, as attention has focused on trying to optimise the reactions to give either tetrols or pentols. This

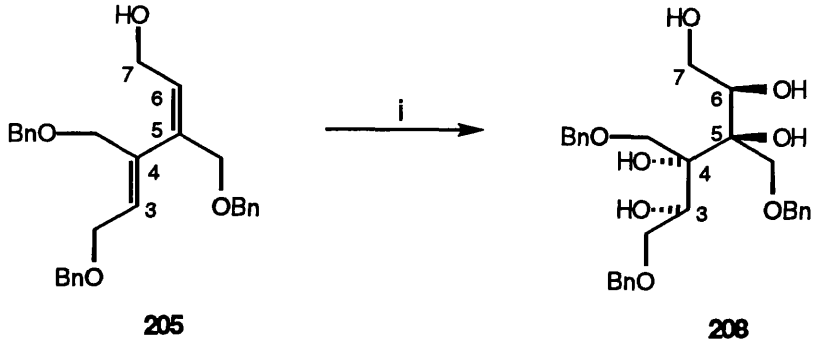
has required running the majority of the AD reactions in increased concentrations, and it has been suggested that this affects the enantiomeric excesses of the products.[46]

By this stage we had become aware that it would be easier to perform the reaction in the one-phase NMO system in order to obtain directly the tetraols and pentaols. Although our initial efforts at a one-pot double AD reaction in the two-phase system never yielded much of the desired tetraols or pentaols, much knowledge had been gained from these initial experiments which would prove invaluable in the future (*vide infra*).

2.7 One-phase AD of 1,3-diene

As soon as we were aware that exhaustive dihydroxylation would be easier in the homogeneous NMO process, we focused our attention on the one-phase system using the dienic alcohol **205** and its derivatives.

Thus, when the dienic alcohol **205** was subjected to 1 mol% OsO_4 and 5 mol% $(DHQD)_2$-PHAL in the presence of three equivalents of NMO in the homogeneous acetone/water system,[95] the pentaol **208** was obtained as an 8:1 diastereomeric mixture in 74% yield after a total of 6d (Scheme 91).

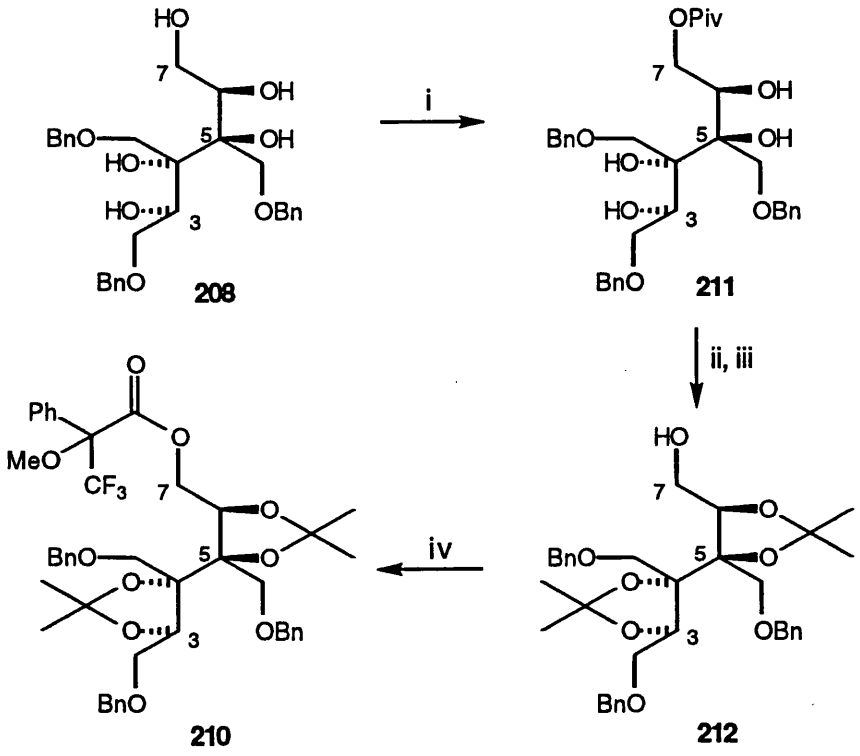


205 **208**

Scheme 91

Reagents and conditions: i) 1% OsO_4 and 5% $(DHQD)_2PHAL$, 3 eq NMO, acetone/water (5:1), RT, 6d, 74%.

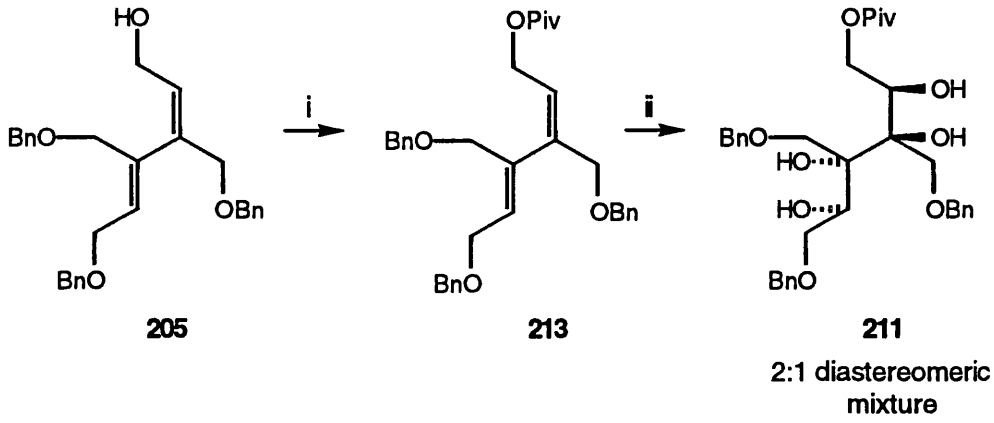
Unfortunately the enantioselectivity of this one-pot procedure was low, giving pentaol **208** in only 24% *ee*. The *ee* of **208** was measured by ^{19}F NMR analysis of the Moshers' ester derivitive **210** which was prepared according to Scheme 92.[100] Since a prior attempt to protect the TBS protected ether **204** as a bis-acetonide derivative resulted in cleavage of the silyl ether, we decided to selectively protect the primary alcohol as the pivalate ester **211**. Thus, treatment of **208** with PivCl, pyridine and catalytic DMAP in CH_2Cl_2 afforded the pivaloate ester **211** in 77% yield. Formation of the bis-acetonide with 2-methoxypropene and cat. *p*-TsOH followed by reductive removal of the pivaloate ester with DIBAL-H afforded the *bis*-acetonide alcohol **212**. Only at this stage was it possible to separate the traces of the minor diastereomer from the dihydroxylation step by FCC. Treatment of **212** with (R)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid, DCC and DMAP (cat.) in CH_2Cl_2 afforded the Moshers ester derivative **210** in quantitative yield.



Scheme 92

Reagents and conditions: i) PivCl, pyridine, CH_2Cl_2, 5 mol% DMAP, 22h, 77%; ii) 2-methoxypropene, *p*-TsOH (cat.), DMF, RT, 17h, 80%; iii) DIBAL-H, CH_2Cl_2, -78°C, 91%; iv) (R)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid, CH_2Cl_2, DCC, DMAP (cat.), RT, 16h, 100%.

The bis-acetonide alcohol **212** was itself required in the synthesis since selective oxidation of the C7 alcohol was required for addition of an acyl anion equivalent to install the C1 sidechain. It was thought that the overall yield of the steps involved in going from the diene **205** to the bis-acetonide alcohol **212** could be improved if the dienic alcohol **205** was protected as the pivaloate ester **213** *prior* to the AD. It was thought that the resulting tetraol would be less water soluble than the corresponding pentaol which would ease the extraction process during work-up. This protection of dienic alcohol **205** would also negate the need for selective protection, which currently proceeded in only 77% yield. Thus, the pivaloate ester **213** was prepared in 97% yield by treatment of **205** with PivCl, pyridine and catalytic DMAP in CH_2Cl_2 (Scheme 93). However, submitting **205** to the one-phase AD generated an interesting result. Not only did the reaction proceed at a greatly reduced rate compared to the dienic alcohol **205**, resulting in only a 37% yield of tetraol **211**, but the diastereomeric ratio of the products had been dramatically reduced from 8:1 to 2:1.



205 **213** **211**

2:1 diastereomeric mixture

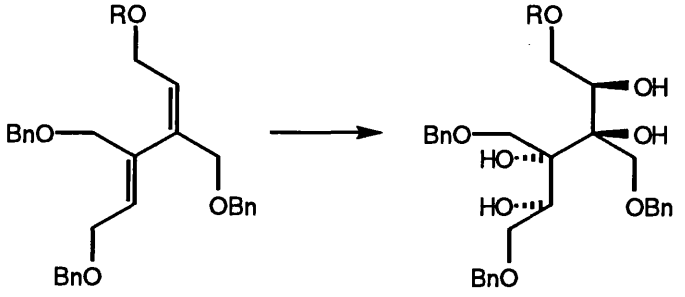
Scheme 93

Reagents and conditions: i) PivCl, pyridine, CH_2Cl_2, 5 mol% DMAP, 16h, 97%; ii) 1% OsO_4 and 5% $(DHQD)_2PHAL$, 3 eq NMO, acetone/water (5:1), RT, 5.5d, 37% as a 2:1 diastereomeric mixture.

For completeness, the TBS protected derivative **201** was also submitted to the one-phase AD. Again, similar results were observed; a greatly reduced rate of reaction, and a greatly reduced d.e. These observations, that the nature of the protecting group not only affected the rates but also the diastereoselectivity of the process, were surprising since the hydroxyl group is expected to lie in the NE quadrant of the Sharpless mnemonic, generally regarded as a "sterically neutral" region. As mentioned earlier, the enantioselectivity of the

one-pot process for the dienic alcohol **205** was low. However, Corey had recently reported that protection of allylic alcohols as their *p*-methoxybenzoate esters resulted in greatly increased enantioselectivity in the two-phase ferricyanide system.[101] We therefore hoped that protection of the dienic alcohol **205** as its PMB ester **214** would increase the *ee* in our one-phase system. Unfortunately, subjecting PMB ester **214** to the NMO/acetone/water system resulted in only a slight increase from 24% ee to 29% ee. The low enantioselectivities observed in our one-pot systems are presumably due to the inherent problems associated with the second catalytic cycle as discussed previously (Scheme 76). The results of the one-pot AD are summarised in Table 8.

Table 8: Results of one-pot Double AD‡



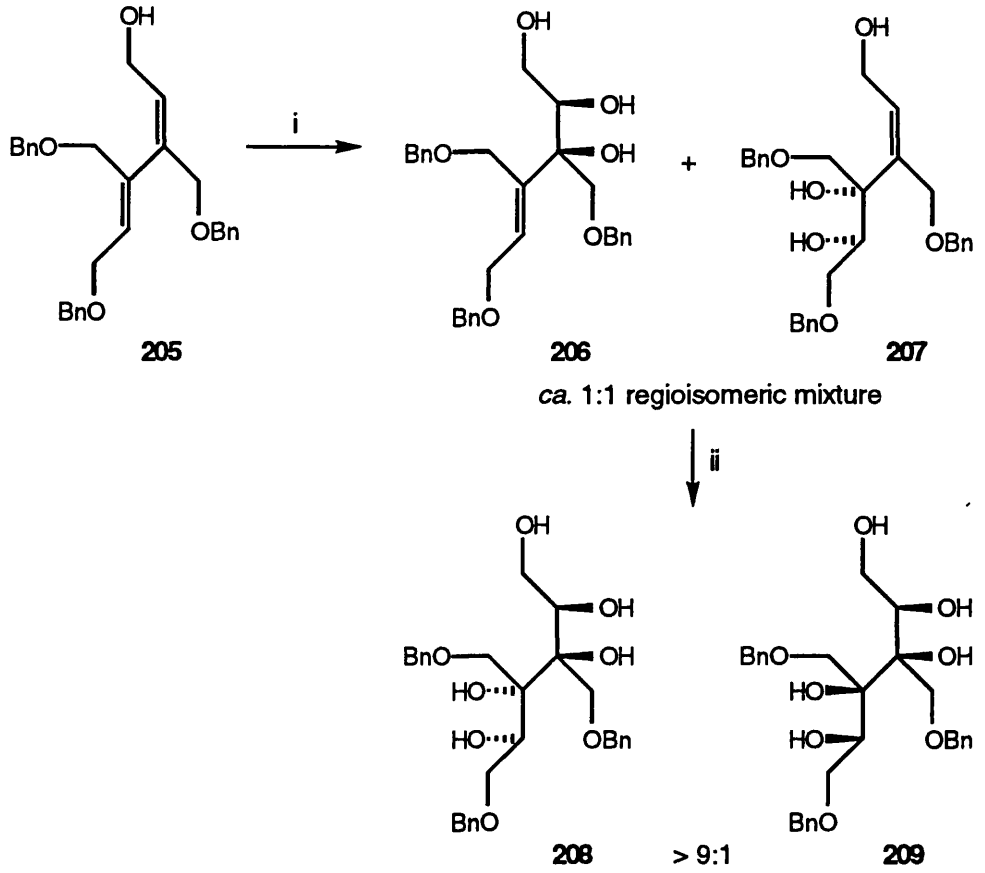
213 R=Piv
201 R=TBS
205 R=H
214 R=(4-MeO)C_6H_4CO

Entry	Diene	Ratio of diastereomers[a]	ee (%)[b]	Yield (%)
1	**213**	2:1	†	37
2	**201**	3:1	†	59
3	**205**	8:1	24	74
4	**214**	†	29	76

‡ Conditions: 1 mol % OsO_4, 5 mol % $(DHQD)_2$-PHAL, 3 eq. NMO, 5:1 acetone : H_2O, rt.
a Estimated by integration of crude ^{13}C NMR with pulse delay 10 s.
b Measured by NMR analysis of the Mosher's ester derivative of compound **212**.
† not measured.

In order to improve the enantioselectivity we adopted a new modification of the AD reaction. Thus, dienic alcohol **205** was subjected to dihydroxylation with Super AD-mix-β under the two-phase ^tBuOH/water system (Scheme 94). We drew on our valuable knowledge

gained from our initial attempts to optimise the reaction (see Section 2.10) by addition of two equivalents $K_2S_2O_8$ as additional co-oxidant along with two equivalents $MeSO_2NH_2$ and 5 mol% $(DHQD)_2$-PHAL and 1 mol% OsO_4. This afforded *ca.* 1:1 mixture of regioisomeric triols **206** and **207** in 78% yield. The second dihydroxylation was now carried out in the one-phase system by exposure of the *unprotected* triols **206** and **207** to 1 mol% OsO_4, 5 mol% $(DHQD)_2$-PHAL and two equivalents NMO in acetone/water. This afforded the pentaol **208** in 58% yield with good diastereoselectivity (>9:1) and with much improved enantioselectivity (76% *ee*).

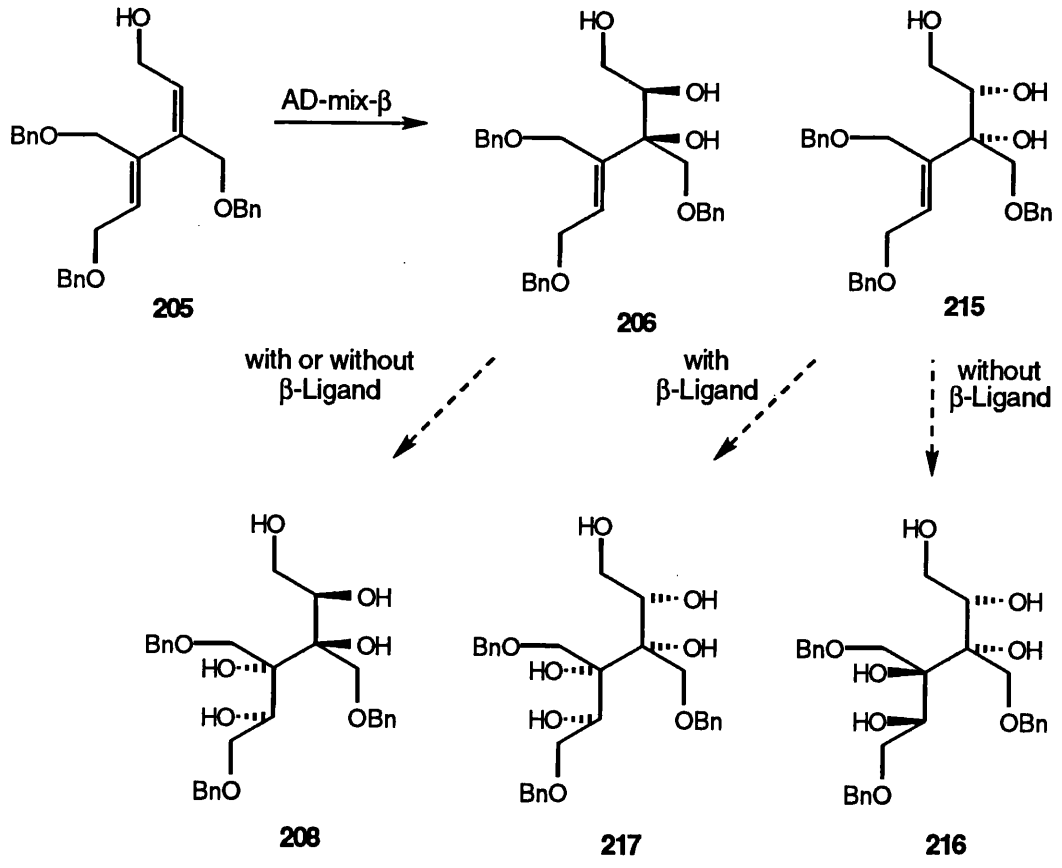


Scheme 94: Revised AD procedure

Reagents and conditions: i) AD-mix-β, 1 mol% OsO_4, 5 mol% $(DHQD)_2PHAL$, 2 eq $CH_3SO_2NH_2$, 2 eq $K_2S_2O_8$, $^tBuOH/H_2O$ (1:1), 0°C to RT, 4d, 78%; ii) 1 mol% OsO_4 and 5 mol% $(DHQD)_2PHAL$, 3 eq NMO, acetone/water (5:1), RT, 58%.

We deliberately left the hydroxyl functionalities of **206** and **207** unprotected to exploit the rate enhancement obtained due to the favorable hydrogen bonding interactions with the trioxo Os(VIII) species. In addition, we had included the $(DHQD)_2PHAL$ ligand in the second dihydroxylation with the aim to overall amplify the *ee* at the expense of the *de* by

creating a mismatch between the wrong enantiomer from the first dihydroxylation and the ligand. However, if all the second dihydroxylation step proceeds through the trioxo Os(VIII) species, then the ligand would not be involved, but it is conceivable that the "normal" pathway could be operating to some extent in this different solvent system. The idea, as applied to our diene **205**, is highlighted in Scheme 95. For clarity, only one regioisomeric triol is shown, but the argument is identical for both triols. Also, simplification is made by assuming the *anti-* diastereoselectivity for the second step to be complete. The first dihydroxylation leads to the two enantiomers **206** and **215**. If the second dihydroxylation was performed in the absence of the $(DHQD)_2PHAL$ ligand, then **206** and **215** would be converted into **208** and **216**, respectively, and the *ee* of the product pentaol would be identical to the *ee* of the intermediate triol. In the presence of the $(DHQD)_2PHAL$ ligand, **206** would still be converted into **208**. However, for **215**, a "mismatch" would exist, and a mixture of **216** and the diastereomer **217** would result. Since less of the "wrong" enantiomer **217** is formed, the *ee* of the pentaol would be increased. The *de*, however, would be lowered due to formation of **217**.



Scheme 95

In order to test this notion, the second step was performed in the absence of the chiral $(DHQD)_2PHAL$ ligand, using quinuclidine in its place. However, the reactions involving quinuclidine were very slow and never proceeded to completion. For this reason, very little material was obtained, and since the hypothesis requires the reaction to have proceeded to completion to obtain a meaningful comparison, it was not possible to determine the ee of the resulting pentaol with this approach.

Nonetheless, we were contented that our new modification gave good yields of the desired pentaol with good enantioselectivity. However, although the first two-phase reaction was reliable, it was very slow and hence conditions were sought to optimise the reaction still further. It was found that use of the more water soluble $Na_2S_2O_8$[102] instead of $K_2S_2O_8$ in combination with additional $MeSO_2NH_2$ and OsO_4 and ligand dramatically reduced the reaction times. Thus, subjecting the dienic alcohol **205** to 5 mol% OsO_4, 7 mol% $(DHQD)_2$-PHAL, two equivalents $Na_2S_2O_8$ and four equivalents $MeSO_2NH_2$ in ^tBuOH/water at RT now afforded the regioisomeric triols **206** and **207** in 70% yield in the greatly reduced time of 18h (cf 4d). Treatment of the triols **206** and **207** with now 3 mol% OsO_4, 6 mol% $(DHQD)_2$-PHAL with three equivalents NMO in acetone/water for 2d afforded the pentaol **208** in 67% yield. The overall yield for the process of converting the diene **205** to the pentaol **208** remained the same (45%) but the reaction time had been reduced from 7.5d to 2.5d. However, it was noticed that these new conditions led to a slight decrease in ee of the pentaol (68% ee).

It is interesting to compare the AD of diene **205** to that of the Nicolaou AD of diene **90** (Section 1.5.2, Scheme 25) which gave the corresponding diol initially in 78% ee and 20% yield, which was later improved to 86% ee and 30% yield. However, our AD does not suffer from such poor yields. The use of either $Na_2S_2O_8$ or $K_2S_2O_8$ has clearly made a significant difference, as well as the rate enhancement of having a free hydroxyl group in the allylic position in the NE quadrant, a result previously unprecedented.[103] In addition to this, our AD has established that the NE quadrant may present more of a steric barrier than previously thought. However, there is no evidence to prove that our diene occupies the mnemonic as we might expect. Our assignment of absolute configuration rests on the assumption that, in the Sharpless mnemonic, the hydrogen substituent on either double bond of the 1,3-diene would

be expected to occupy the "south eastern" quadrant, with the $(DHQD)_2$-PHAL ligand then attacking from the β-face. The outcome of a similar asymmetric dihydroxylation in the Nicolaou synthesis[31] (Section 1.5.2, Scheme 25) is in accord with this assumption. Also, comparison of the optical rotation of the natural product obtained synthetically from our material to that of the isolated natural product itself, would determine the absolute stereochemistry of our AD process.

This AD methodology directed at polyol synthesis clearly has immense potential in a wide variety of synthetic applications. For example, one could imagine access to a series of unnatural sugars *via* use of the appropriate chiral ligand with the above polyol methodology. Normally, several steps are required to manipulate carbohydrates into synthetically useful fragments. Here, Stille coupling followed by double AD could give properly protected/functionalised pieces directly.

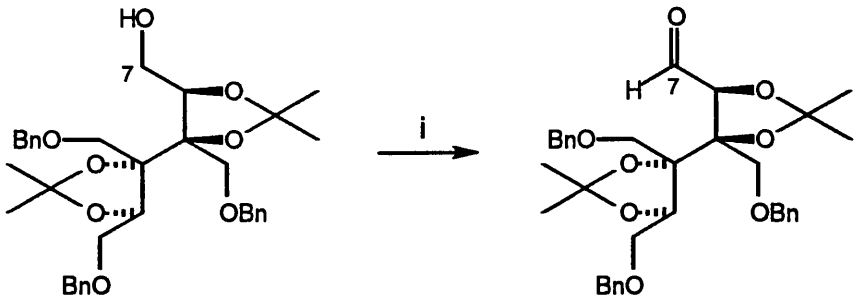
With the double AD now optimised, the remaining steps in the synthesis of the model core could be investigated.

2.8 Synthesis of the acyclic precusor of the bicyclic core.

With sufficient quantities of pentaol **208** in hand, the synthesis was once again able to move forward.

Oxidation of the bis-acetonide alcohol **212** (prepared according to Scheme 92) to the aldehyde **218** initially proved problematic. Attempts using PCC, TPAP or an old batch of the Dess-Martin periodinane reagent gave no reaction. Freshly prepared Dess-Martin periodinane reagent gave a single non-aldehyde product, the structure of which was initially unknown (although it was later thought to be understood what had occurred, *vide infra*). It had recently been reported that *o*-iodoxybenzoic acid (the intermediate in the Dess-Martin periodinane preparation) in anhydrous DMSO was a useful reagent for oxidation of alcohols to aldehydes, but this also proved unfruitful. Swern oxidation[106] using $(COCl)_2$/DMSO in CH_2Cl_2 offered a significant improvement giving aldehyde **218** in 61% yield. However, this method suffered from α-epimerisation upon warming the reaction mixture from -78°C after addition of triethylamine. This problem was remedied by quenching the reaction at -78°C

with aqueous NH_4Cl one hour after addition of triethylamine at -78°C. This procedure afforded pure aldehyde **218** in 83% yield (Scheme 96).



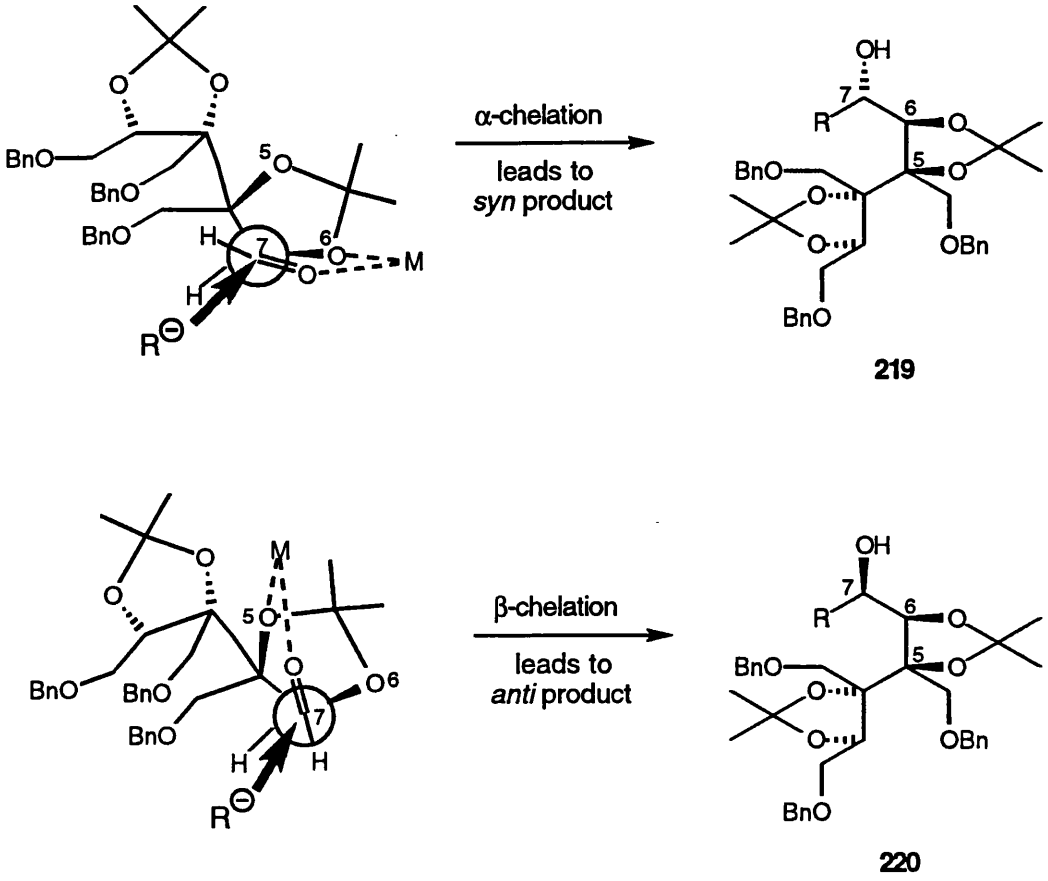
212 **218**

Scheme 96

Reagents and conditions: i) $(COCl)_2$/DMSO, CH_2Cl_2, -78°C then Et_3N, -78°C, 1h, 83%.

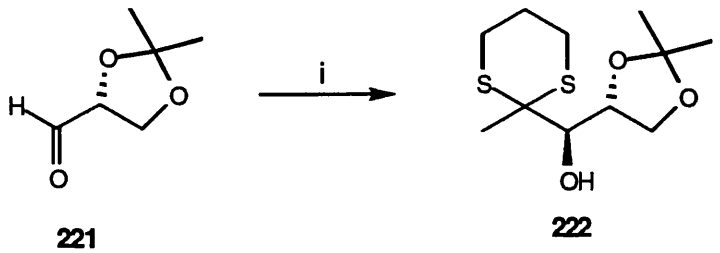
We now needed to install our C1 carbon substituent by means of an acyl anion equivalent. As can be seen in Scheme 97, the chelation control model[106] predicts the desired diastereomer **219** if chelation occurred at the C6 oxygen, *i.e.* α-chelation. However, chelation at the C5 oxygen, *i.e.* β-chelation, would lead to the C7 epimer **220**, which would result in the bicyclic core possessing the wrong stereochemistry at C7.

Aldehydes possessing both an α- and β-chelating group often afford low diastereoselectivities when under the chelation control method due to competition at both the α-and β-sites. 2,3-*O*-Isopropylideneglyceraldehyde **221** is one such aldehyde that is notorious for frequently returning low diastereoselectivities upon addition of organometallics operating under chelation control, although the *anti* addition product resulting from β-chelation usually predominates.[107]



Scheme 97

David and co-workers[108] in fact reported that addition of 2-lithio-2-methyl-1,3-dithiane occurred with complete stereocontrol to afford the *anti* product **222** (Scheme 98). This is in accord with the Felkin-Ahn model. Incidentally, for addition to our aldehyde **218**, the non-chelation control Felkin-Ahn model predicted the wrong C7 epimer **220**.

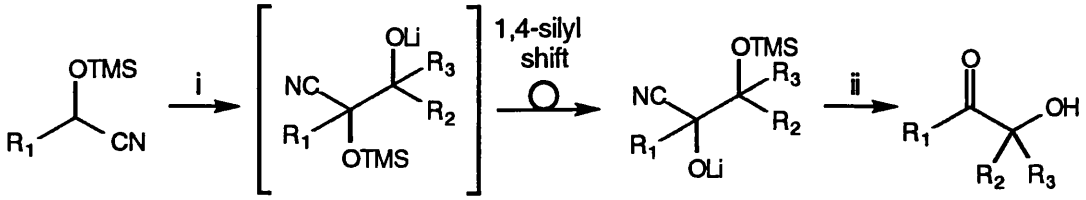


Scheme 98

Reagents and conditions: i) 2-lithio-2-methyl-1,3-dithiane, THF.

Although the α-chelation control model predicted the desired epimer **220**, our initial studies focused on addition of lithiated acyl anion equivalents rather than use of metals usually employed to achieve chelation control.

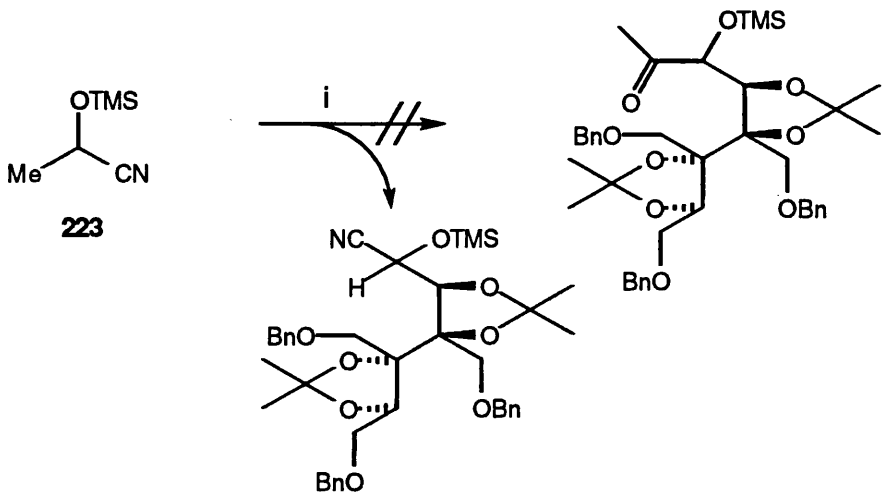
It had been reported that silyl protected cyanohydrins functioned as acyl anion equivalents and could be deprotonated under mild conditions (LDA, -78°C, THF).(Scheme 99).[109] After addition to aldehydes or ketones they underwent a 1,4-silyl transfer followed by elimination of cyanide to give the silyl ethers, which on hydrolysis afforded the hydroxy ketones.



Scheme 99

Reagents and conditions: i) LDA, THF, -78°C, 5 min then R_2COR_3; ii) H_3O^+.

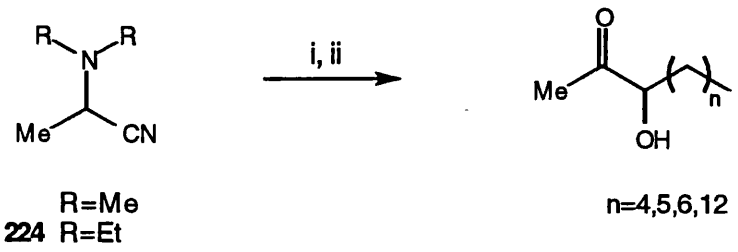
However, we later discovered from the literature that the anion could only be formed if the R_1 substituent was an electron withdrawing group such as aryl or allyl. This was consistent with our observations that treatment of **223** with LDA at -78°C in THF followed by addition of aldehyde **218** led only to addition of TMS-cyanide to the aldehyde (Scheme 100).



Scheme 100

Reagents and conditions: i) LDA, THF, -78°C , then **218**.

Use of dialkylaminonitriles as acyl anion equivalents had also been reported,[110, 111] and aliphatic groups were known to be tolerated. Again, generation of the anion was reported to be achieved under mild conditions (LDA, -78°C, THF), but also regeneration of the ketone could be effected either by the usual acid hydrolysis or by other mild hydrolytic agents such as copper sulfate, iron sulfate, copper acetate or silica gel (Scheme 101).



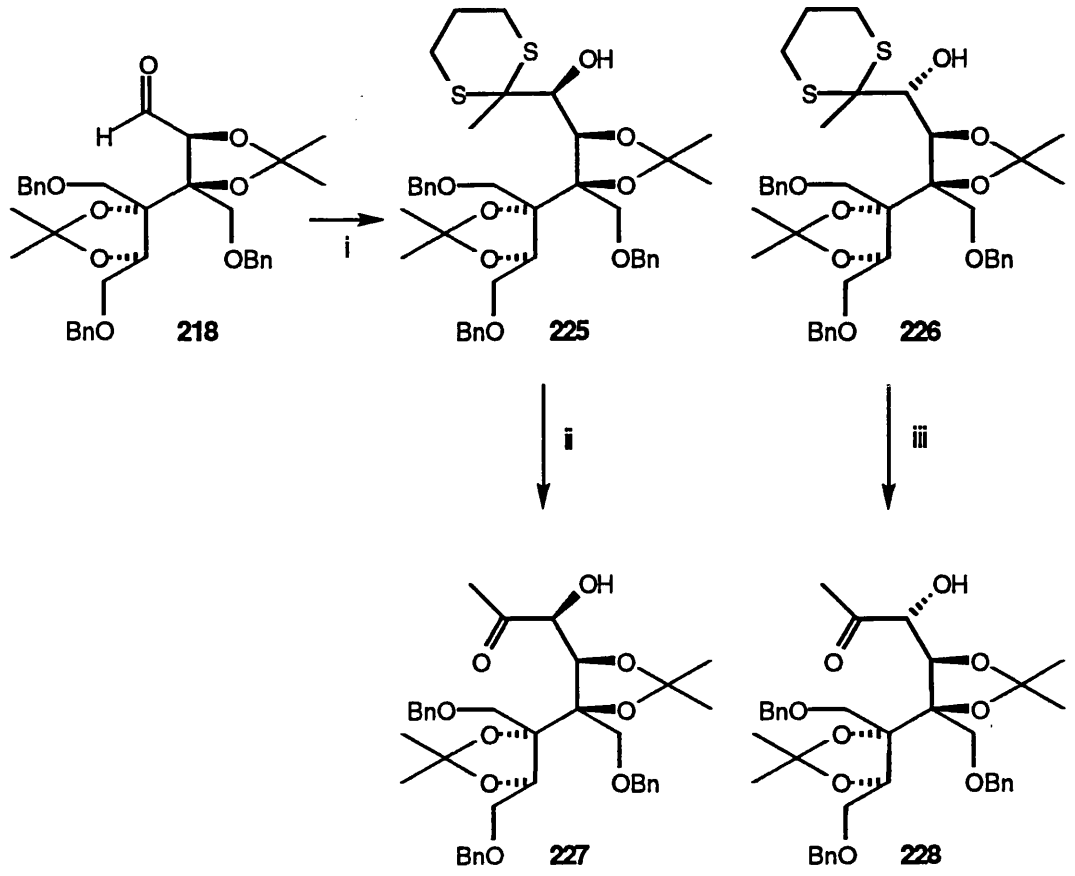
R=Me
224 R=Et

n=4,5,6,12

Scheme 101

Reagents and conditions: i) LDA, THF, -78°C , 5 min then $CH_3(CH_2)_nCHO$; ii) H^+.

Thus the diethylaminonitrile **224** was prepared according to the literature procedure.[112] Unfortunately, we had no success in our attempts to add **224** to the aldehyde **218**. We therefore turned our attention to the anion derived from 2-methyl-1,3-dithiane as our source of acyl anion equivalent.[113] Thus, addition of 2-lithio-2-methyl-1,3-dithiane to aldehyde **218** afforded a 1:1.2 mixture of the diastereomeric alcohols **225** and **226** in 97% yield (Scheme 101). The diastereoselectivity of this reaction was disappointingly low, but the alcohols **225** and **226** were readily separable by FCC. Efforts to increase the diastereoselectivity by addition of chelating metal salts ($MgBr_2$ and $ZnBr_2$) proved unfruitful.



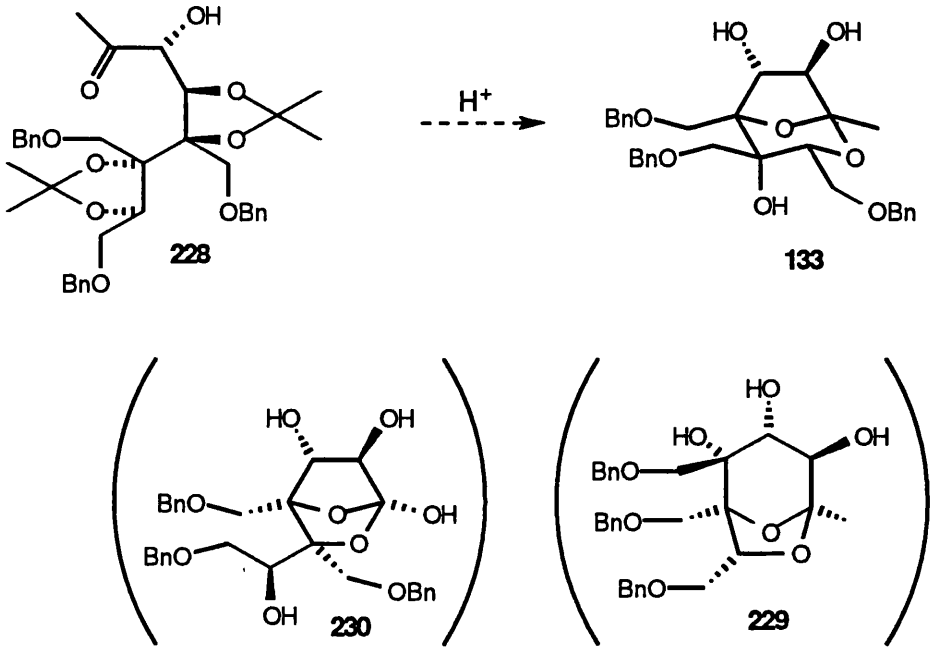
Scheme 102

Reagents and conditions: i) 2-lithio-2-methyl-1,3-dithiane, THF, -78°C, 97%; ii) $Hg(ClO_4)_2$, $CaCO_3$, THF/H_2O (5:1), RT, min, 84%; iii) $Hg(ClO_4)_2$, $CaCO_3$, THF/H_2O (5:1), RT, 30 min, 92%.

The stereochemistry of **225** and **226** was unknown until the correct bicyclic core had been made and confirmed (*vide infra*), and hence the stereochemistry of the addition products could be deduced. Removal of the 1,3-dithiane protecting groups with $Hg(ClO_4)_2$ and $CaCO_3$ proceeded smoothly[114] to afford the acyclic precursors **227** and **228**, and we were now in a position to examine the crucial bicyclic internal ketalisation reaction.

2.9 Cyclisation of the acyclic precursors 227 and 228 to the bicyclic core systems

With the acyclic precursors **227** and **228** in hand, the crucial bicyclic ketalisation was investigated. As mentioned previously, at the start of our work there was no precedent for the formation of the desired bicyclic 1,6-anhydrofuranose ring system by internal ketalisation. It had always been our hope that acid-catalysed treatment of **228** would on thermodynamic grounds lead to the formation of the desired 2,8-dioxabicyclo[3.2.1]octane ring system **133** rather than the 1,6-anhydropyranose or 1,5-anhydrofuranose structural isomers **229** and **230** (Scheme 103).

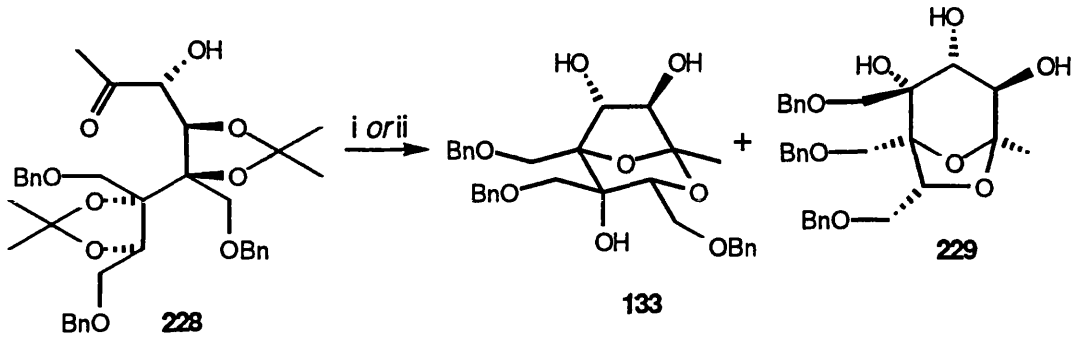


Scheme 103

Molecular modelling studies[115] on minimally substituted cores suggested the 1,6-anhydrofuranose isomer (cf. **133**) to be the most stable of the three possible ketals. While common molecular mechanics force fields are not properly parameterised for these systems, they agreed with semi-empirical calculations that the 1,5-anhydrofuranose isomer (cf. **230**) was much less stable than the other two ketals.

Treatment of the hydroxyketone **228** with 2% HCl/MeOH at 60°C for 18h did indeed afford the desired bicyclic anhydrofuranose ketal isomer **133** in 45% yield, but in addition generated the undesired 1,6-anhydropyranose ketal isomer **229** in 47% yield (Scheme 103). It was found that the ratio improved to 2.5:1 **133**:**229** if the reaction was carried out at RT for

2d, but this resulted in considerably reduced yields (34% of **133**) since the reaction had not reached completion under these conditions. Leaving the reaction longer merely served to increase the amount of **229**.

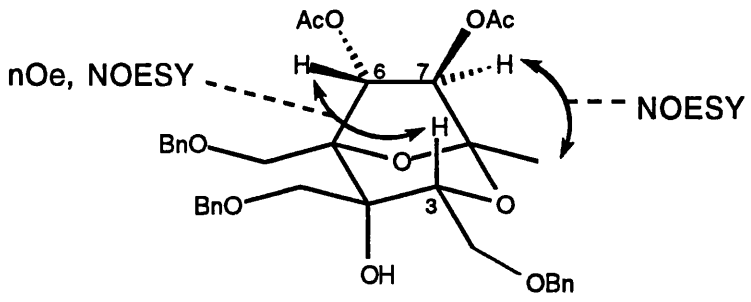


Scheme 104

Reagents and conditions: i) 2% HCl/MeOH, 60°C, 18h, 45% of **133**, 47% of **229**; ii) CH_2Cl_2/TFA/H_2O (20:10:1), RT, 16h, 38% of **133**, 38% of **229**.

Employing the cyclisation conditions used by Evans in his zaragozic acid C synthesis,[33] *i.e*, CH_2Cl_2:TFA:H_2O (20:10:1), resulted in the same 1:1 ratio of **133** to **229** but in slightly lower yields (Scheme 103). Use of 6M HCl in EtOH at RT led to a much more rapid reaction, (tlc indicated mainly just the two cores **133** and **229** after just 5h), but strongly favoured the 1,6-anhydropyranose **229**.

The structure and stereochemistry of **133** were proven by extensive NMR experiments on the derived 6,7-bis-acetate **231** (Figure 18). The ^1H NMR spectrum identified two doublets at 6.01 and 5.11 ppm, corresponding to H6 and H7. The observed J H6-H7 value of 2.8 Hz was characteristic of the desired ring system and of the correct 6R, 7R relative stereochemistry.[116] The ^{135}DEPT experiment identified three CH signals at 81.8, 77.7 and 73.1 ppm. The ^1H-^{13}C correlation experiment identified the CH signals at 81.8 and 77.7 ppm as the acetylated hydroxyls, and hence allowed assignment of the remaining CH signal at 73.1ppm as C3. This then allowed assignment of H3 at 4.43 ppm. Important cross-peaks in the NOESY spectrum were observed between the C1-methyl group and H7, and between H6 and H3. In addition, ^1H NMR difference nOe experiments observed a 14% enhancement of H3 upon irradiation of H6 providing strong evidence for the sense of diastereoselectivity of the dihydroxylation process.

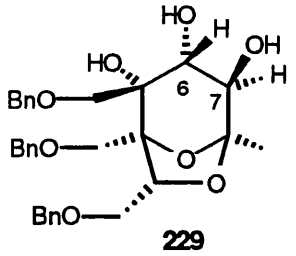


231

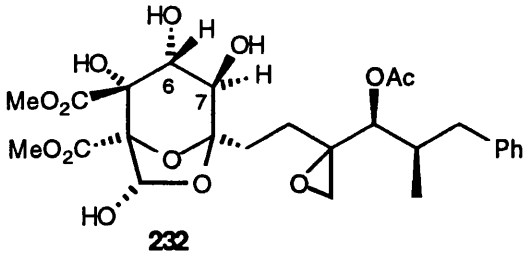
J values	nOe	NOESY
H6-H7; 2.8 Hz	14% H6-H3	H7-C1 Me H6-H3

Figure 18

The isomeric ketal structure **229** was assigned based on its ^{1}H NMR. The relative 6R, 7R stereochemistry resulting from the dithiane addition was established by analogy to the correct core **133** since it was generated from the same hydroxy ketone. The observed J H6-H7 value of 7.8 Hz was characteristic of *trans*-diaxial coupling in a six-membered ring, and was consistent with the reported J H6-H7 coupling constant of 8.0 Hz for the anhydropyranose **232** from workers at Glaxo (Figure 19).[117]



229



232

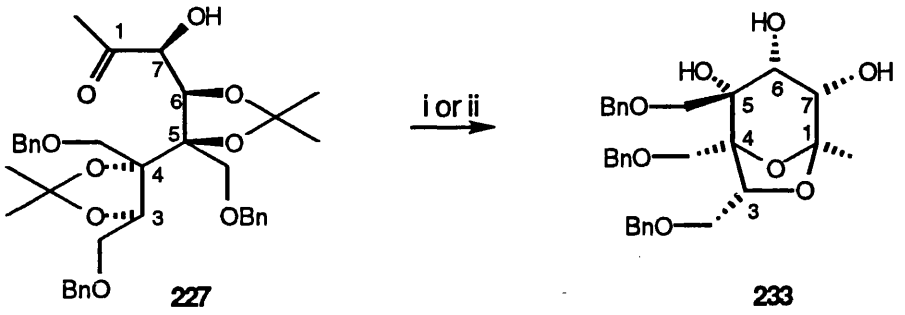
J values	J values
H6-H7; 7.8 Hz	H6-H7; 8.0 Hz

Figure 19

We were satisfied as to which ketal isomer was which based on the ^{1}H NMR J values and 2D-NMR spectroscopic data, but 3-bond HMBC studies would be required for full confirmation.

In investigating the cyclisation of the C7 epimer, a somewhat different result was obtained. To our surprise, treatment of the C7 epi alcohol **227** with 2% HCl/MeOH at either

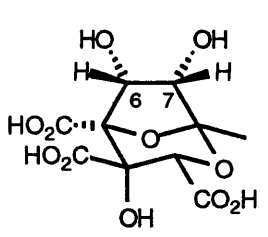
RT or with heating always led exclusively to what appeared to be the undesired 1,6-anhydropyranose ketal isomer **233** (Scheme 105). Cyclisation of **227** under the Evans conditions[33] also gave the same result.



Scheme 105

Reagents and conditions: i) 2% HCl/MeOH, 60°C, 18h, 75%; ii) CH_2Cl_2/TFA/H_2O (20:10:1), RT, 16h, 69%.

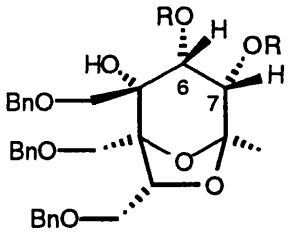
The structure of the 1,6-anhydropyranose **233**, resulting from the C7 epimer of the dithiane addition, was tentatively assigned from the J H6-H7 coupling constants. It had been reported that the 6R, 7S stereochemistry of the natural product had a J H6-H7 value of 6.5 Hz.[116] This was also in accordance with the Nicolaou 6R, 7S model core **234** having a J H6-H7 value of 6.3 Hz.[31d] However, the observed J H6-H7 in both **233** and the derived 6,7-bis-acetate **235** of 4.4 Hz indicated we had the anhydropyranose isomer **233** rather than the isomeric 1,6-anhydrofuranose **236** (Figure 20), though again 3-bond HMBC studies would be required for full confirmation.



234

J values

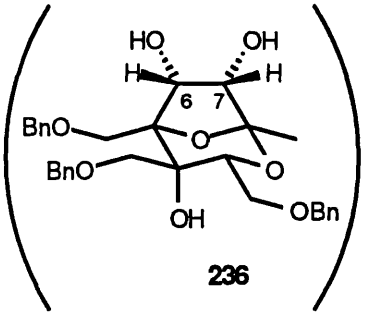
H6-H7; 6.3 Hz



233 R=H
235 R=Ac

J values

H6-H7; 4.4 Hz



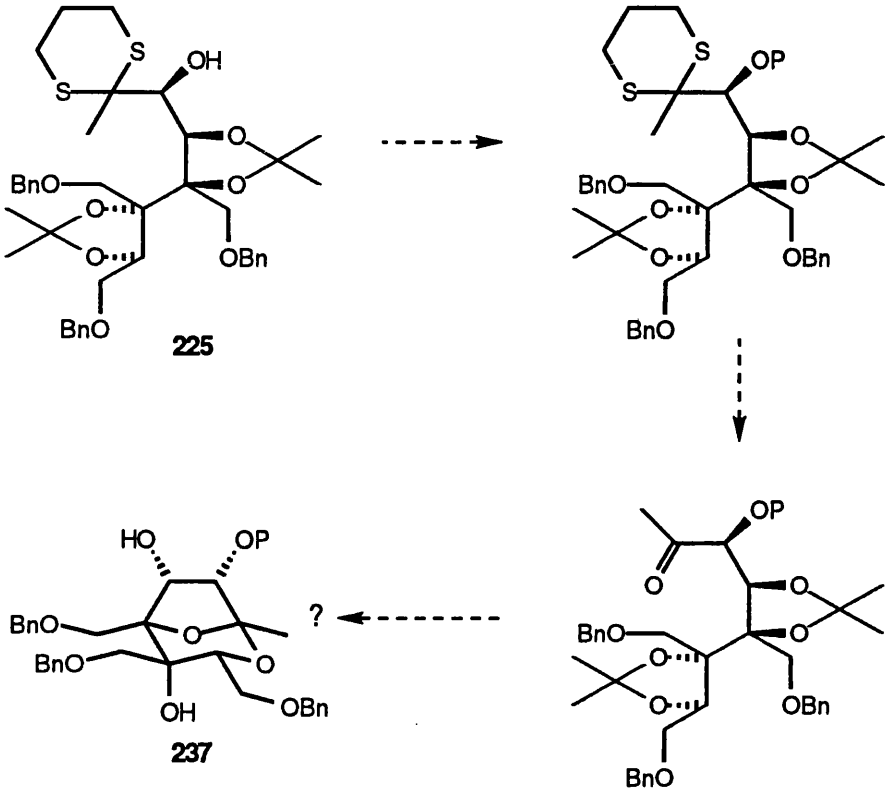
236

Expected J values

H6-H7; *ca.* 6.5 Hz

Figure 20

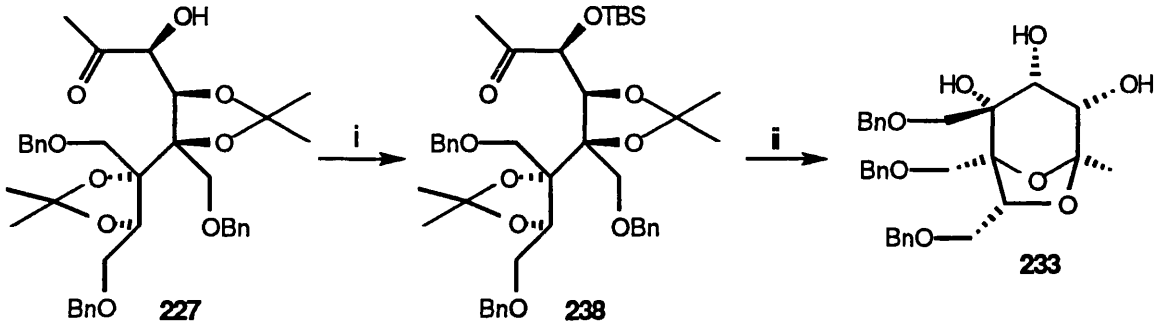
It was thought that the exclusive formation of the anhydropyranose ring system **233** might be as a result of developing hydrogen bonding interactions of the C5-C6-C7 triol functionality. It seemed interesting to test this notion by protecting the C7-hydroxyl prior to the cyclisation thereby reducing the hydrogen bonding interactions and see if this would generate any of the 1,6-anhydrofuranose isomer **237** (Scheme 106).



Scheme 106

However, silylation of **225** with as many as 9 equivalents of TBDPSCl and 12 equivalents of imidazole in DMF at 70°C for several days gave no reaction, as did the use of TBDMSOTf and 2,6-lutidine in CH_2Cl_2. Similarly, treatment of **225** with NaH and MeI in THF gave none of the corresponding methyl ether, returning only starting material. It was thought that the dithiane group was causing severe steric hindrance of the C7 hydroxyl, and that removal of the dithiane to give the keto-alcohol **227** *prior* to protection might alleviate the problem. Again though, attempted silylation of **227** with either TBDPSCl/imidazole in DMF at 70°C, or TBDPSCl, Et_3N and cat. DMAP in CH_2Cl_2 failed to give any reaction. Use of TBDMSOTf and 2,6-lutidine in CH_2Cl_2 gave a mixture of products. The ^1H nmr of one of the less polar products indicated the presence of the TBS group, and though its structure was

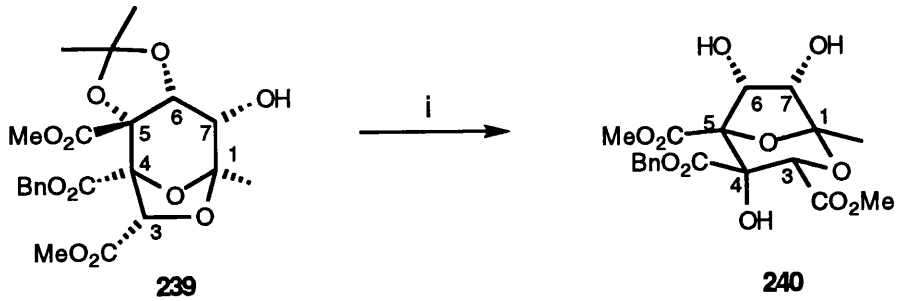
not conclusively known, it was tentatively assigned as **238**. Nonetheless it was submitted to the Evans cyclisation conditions.[33] Tlc analysis showed a polar product that co-ran with the known core **234**, and hence suggested that if the TBS ether had been made, it in any case underwent cleavage in the cyclisation reaction (Scheme 106).



Scheme 107

Reagents and conditions: i) TBSOTf, 2,6-lutidine, CH_2Cl_2; ii) CH_2Cl_2/TFA/H_2O (20:10:1), RT, 4h.

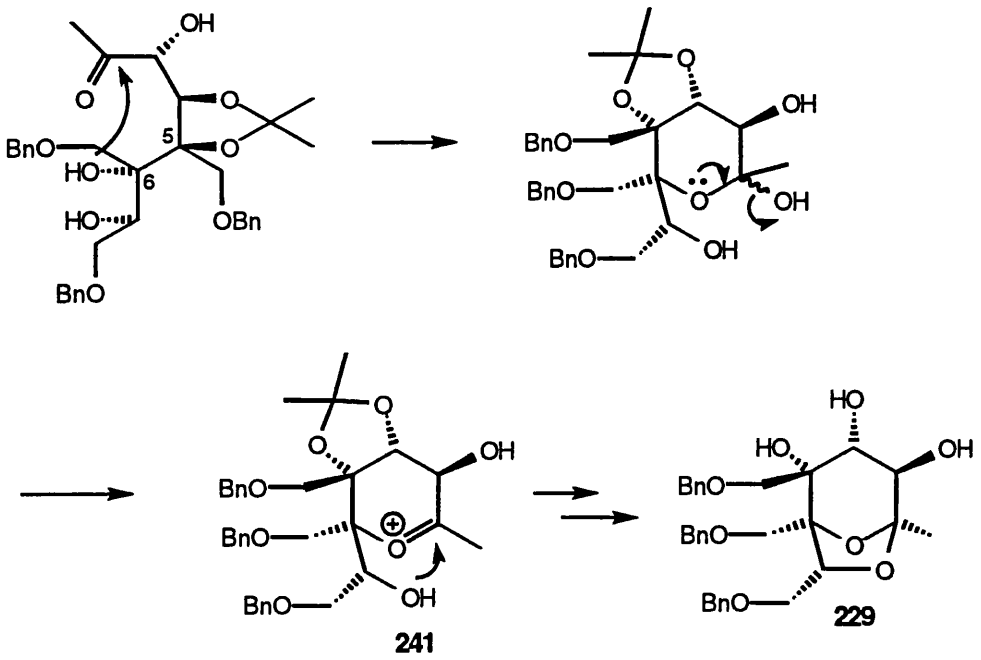
Returning to the correct C7 core, we initially thought that the cyclisation would be under thermodynamic control. To test this notion, the isolated cores were resubmitted to the reaction conditions. Thus, separate treatment of **133** and **233** with 2% HCl/MeOH at 70°C showed no change by tlc after 4h. Likewise, treatment of **229** with 2% HCl/MeOH at 70°C for 2h, then RT for 3d indicated none of the other core system at any stage by tlc. Thus, the cyclisation would appear to be kinetically controlled. This would appear contrary to Nicolaou's cyclisation of the incorrect C7 epimer **239**, since re-submission of the anhydropyranose **239** (isolated if the reaction was not allowed to proceed to completion) to the reaction conditions resulted in further rearrangement to the 1,6-anhydrofuranose **240** (Scheme 108).[31d] However, none of the analogous anhydropyranose with the correct C7 stereochemistry was isolated to establish if this rearrangement also occurred for the correct C7 system.



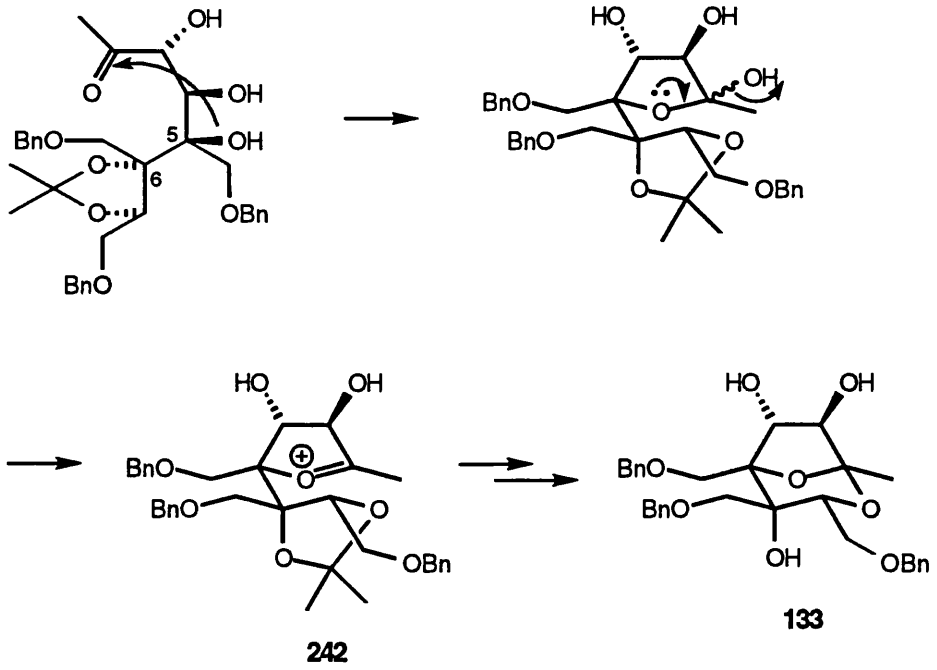
Scheme 108

Reagents and conditions: i) 2% HCl/MeOH, 68°C, 9h, 59%.

Leading on from our cyclisation studies, it was obviously desirable to increase the ratio of the 1,6-anhydrofuranose isomer **133** over the 1,6-anhydropyranose isomer **229**. We wondered what factors might be governing the observed ratio, and what could be done to improve it. Our control experiments had established that the cores did not equilibrate and hence suggested our cyclisation to be under kinetic control (cf. Evans).[118] The factors influencing the cyclisation are clearly complex, and since the intermediates cannot be characterised, ideas are difficult to prove. It is not known whether the acetonide cleavage or cyclisation itself is the rate determining step. However, it is conceivable that the relative rate of acetonide removal could influence the cyclisation in so far as if the C3-C4 acetonide was removed first, then the cyclisation might occur to give the undesired anhydropyranose **229** *via* the oxonium ion **241** (Scheme 109). Conversely, if the C5-C6 acetonide was removed first, then the correct ketal core **133** might occur *via* the oxonium ion **242** (Scheme 110).

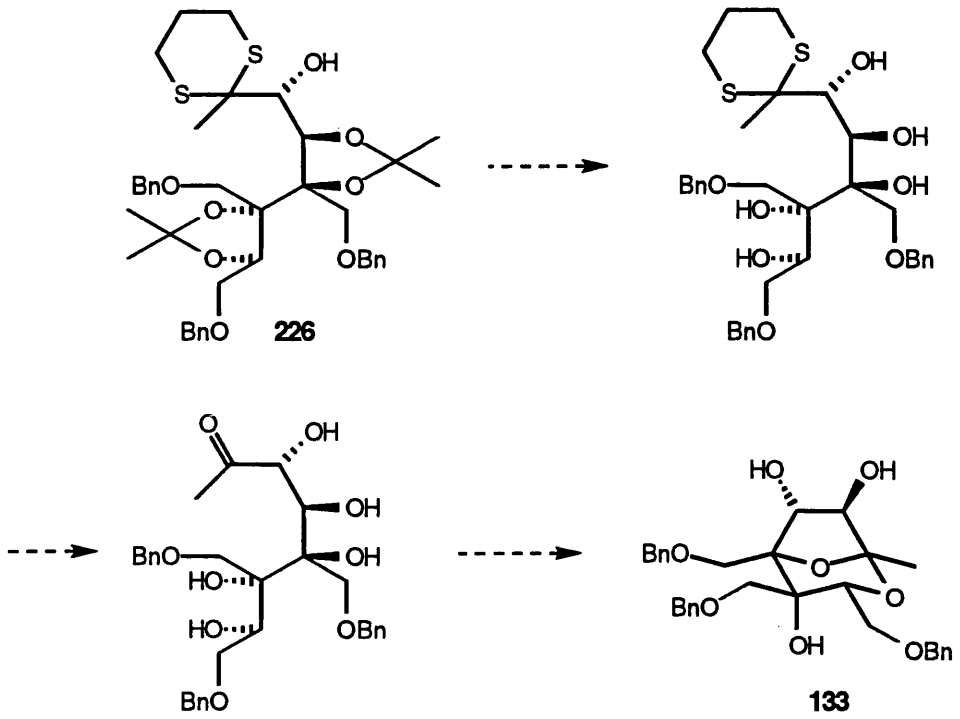


Scheme 109



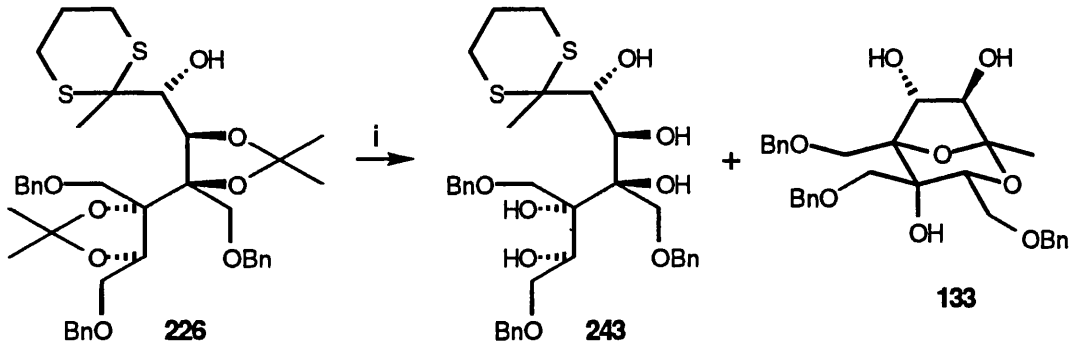
Scheme 110

Therefore, we sought to remove this additional factor, so that only the intrinsic relative tendency of the hydroxyls to cyclise is operating, by deprotecting the dithiane *after* the acetonides, as depicted in Scheme 111.



Scheme 111

In the event, both acetonides of **226** proved to be extremely robust towards acid hydrolysis, but with one of the acetonides very much more so than the other. Treatment of **226** with 50% aqueous TFA in THF did not effect the hydrolysis. Use of $Pd(MeCN)_2Cl_2$ in acetone as developed by Lipshutz[119] gave mainly starting material after 3d, and as ever increasing amounts of Pd were added, tlc indicated a multi-component mixture. Use of the Evans cyclisation conditions proved more effective, although very slow (Scheme 112). After 16h, all the starting material had been consumed, and two new products were observed by tlc. As time progressed the less polar component was converted into the more polar compound. The reaction was left until all the less polar compound had been converted into the more polar of the two spots (2d), by which time a small amount of an even more polar component was observed. At this stage the reaction was worked up and the two components were isolated. The ^1H NMR was consistent with the major product being the desired pentaol **243**, isolated in 35% yield. The second isolated product was the bicyclic core **133**, isolated in 31% yield.



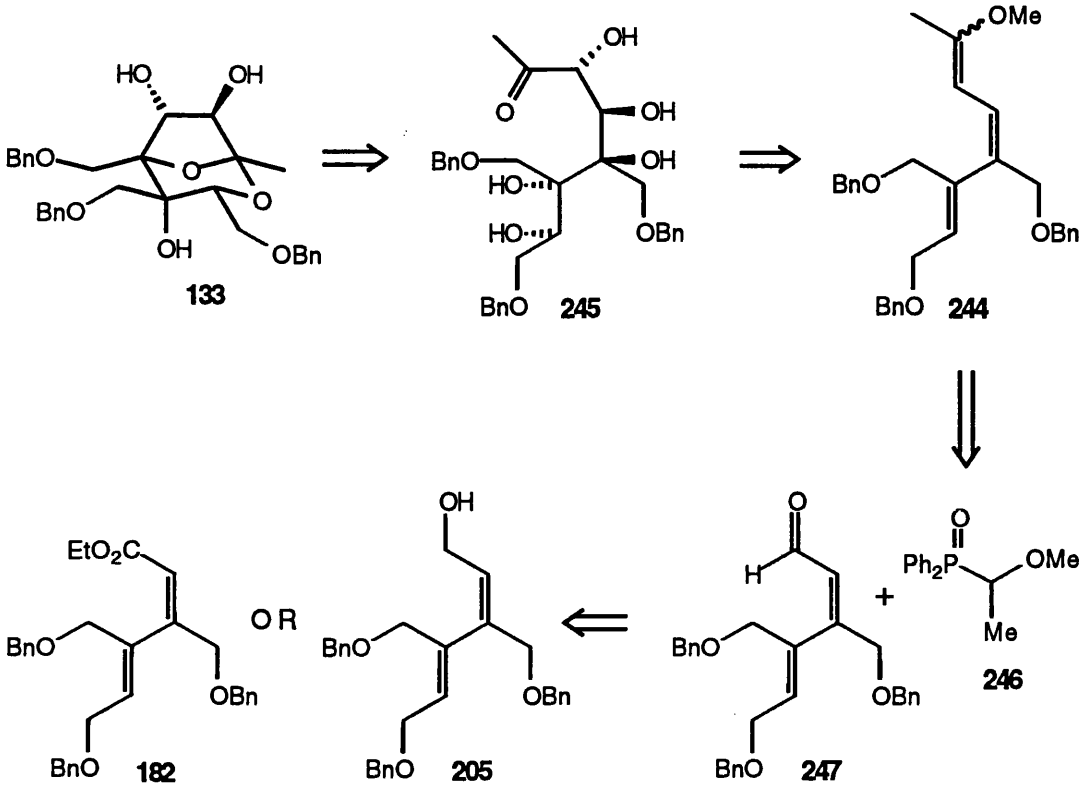
Scheme 112

Reagents and conditions: i) CH_2Cl_2/TFA/H_2O (20:10:1), RT, 2.75d, 35% **243**, 31% **133**.

Interestingly, none of the other isomeric core **229** was detected. It would seem that under the extended duration of the reaction, once at the pentaol **243**, the dithiane had also been hydrolysed liberating the ketone for cyclisation. It was encouraging to find that only the desired core **133** was observed, and these preliminary results would seem to support our hypothesis. The very small amounts of **243** were subjected to $Hg(ClO_4)_2$ and $CaCO_3$. A single product was obtained, but the ^1H NMR of the crude product indicated no presence of the characteristic methyl group at *ca.* 2ppm, indicating the loss of the ketone functionality. It appeared that either the C5 or C6 hydroxyl had cyclised onto the ketone. Unfortunately there were insufficient amounts of material to obtain proper characterisation and this deprotection approach may be the subject of future investigation.

2.10 Efforts aimed at improving stereocontrol of the C7-hydroxyl: the triene approach.

In light of the poor diastereoselectivity observed in the dithiane addition reaction, it was envisaged that the C7 hydroxyl could be installed by AD methodology at the same time as the C3 to C6 stereocentres *via* a triple AD of triene **244** to give the keto-pentaol **245** (Scheme 113).



Scheme 113

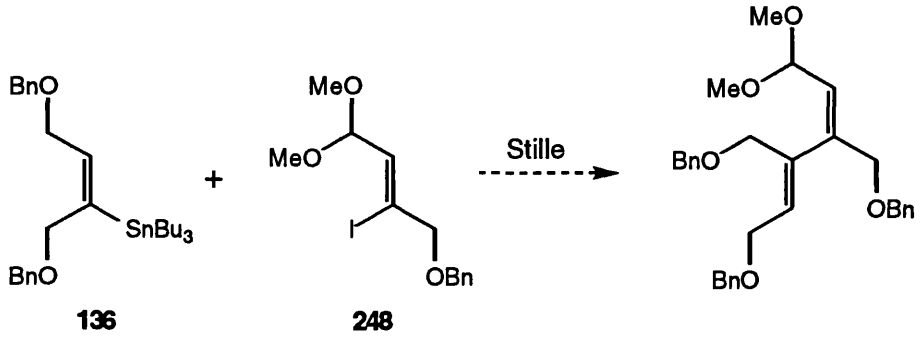
The same $(DHQD)_2PHAL$ ligand would be required to achieve the correct face selectivity for all three olefins. This route is extremely attractive since not only would it incorporate all 5 stereocentres from C3 to C7, it would also negate the need for acetonide protecting groups and hence makes for an extremely efficient synthesis of the bicyclic core **133**. While this has yet to be achieved, some preliminary investigations were performed and these are described here.

It was thought that synthesis of the triene **244** could be achieved using Wittig methodology by addition of the known[120] phosphine oxide **246** to the aldehyde **247**. Aldehyde **247** itself could arise either from reduction of the dienic ester **182**, or by oxidation of the alcohol **205**.

Initial attempts at reduction of the dienic ester **182** with DIBAL-H at -78°C in CH_2Cl_2 always progressed directly to the alcohol **205** without ever any indication of the aldehyde **247** by tlc. Reduction of esters with $LiAlH_4$ in the presence of Et_2NH had been reported to stop at the aldehyde level without further reduction to the alcohol,[121] but these conditions also reduced **182** directly to the alcohol **205**. We therefore investigated the oxidation of alcohol **205**.

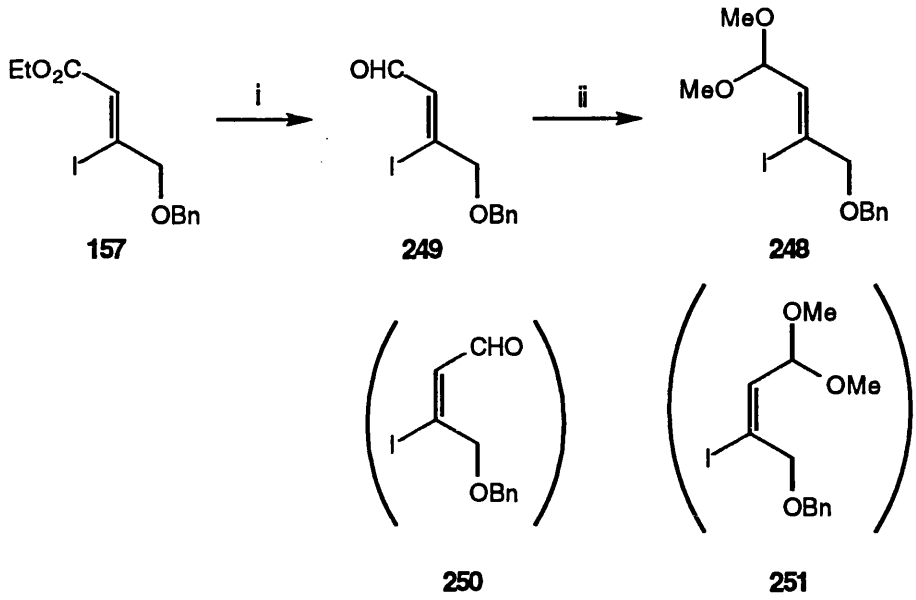
Oxidation of **205** with TPAP, Dess-Martin periodinane, TEMPO,[122] PCC and Collins reagent all gave the same results. In all cases, tlc indicated two new products, which when individually isolated and purified by FCC appeared as a mixture in the ^1H NMR as two aldehydes and another unidentifiable product. Immediate tlc analysis of the NMR samples indicated that what was once a single spot now appeared as the same two spots. It became apparent that some kind of interconversion process was taking place, and this led us to approach the synthesis of aldehyde **247** in a different manner.

We opted for an approach based on a Stille coupling with a vinyl iodide fragment that already contained the aldehyde functionality, in fact, protected as the acetal **248** (Scheme 114).



Scheme 114

The vinyl iodide **248** was prepared according to Scheme 115. DIBAL-H reduction of **157** at -78°C gave the aldehyde **249** along with what was presumed to be the isomerised aldehyde **250** (tlc) since aldehydes of this nature had been reported to be unstable and prone to isomerisation.[123] For this reason, the aldehyde **249** was not purified but submitted directly into the next step. Thus, treatment of the crude reaction mixture with trimethyl orthoformate in the presence of catalytic PPTS in MeOH gave the corresponding hemi-acetal **248** as the major product in an overall yield of 69%, along with the readily separable **251** as the minor product, (which also contained an inseparable contaminant).



Scheme 115

Reagents and conditions: i) DIBAL-H, CH_2Cl_2, -78°C, 15 mins; ii) $CH(OMe)_3$, MeOH, 10 mol% PPTS, 69% **248** overall.

The stereochemistry of **248** was proven by an nOe difference experiment which showed a large nOe between the olefinic proton and the vinylic methylene protons (Figure 21).

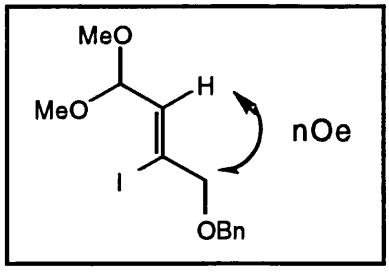
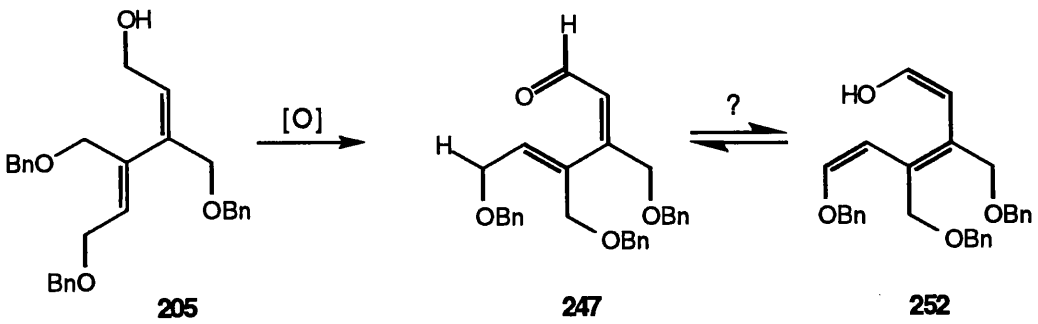


Figure 21

A co-worker[49] later found that the isomerisation during the DIBAL-H reduction could be avoided, enabling **248** to be obtained cleanly and in high yield. The same co-worker found that the ^1H NMR of the crude reaction mixture resulting from coupling of **248** with the vinyl stannane **137** used in our core synthesis, under our optimised Stille conditions, was identical to that obtained from oxidation of the dienic alcohol **205**. It was later found[49] that there was possibly an equilibrium between the aldehyde **247** and the enol isomer **252**, though this was never fully established (Scheme 116).



205 247 252

Scheme 116

It seemed logical that during the Stille coupling, the acetal functionality had probably been hydrolysed due to the presence of the added $ZnCl_2$, liberating the aldehyde functionality (either before or after the coupling had taken place), which would account for the observations.

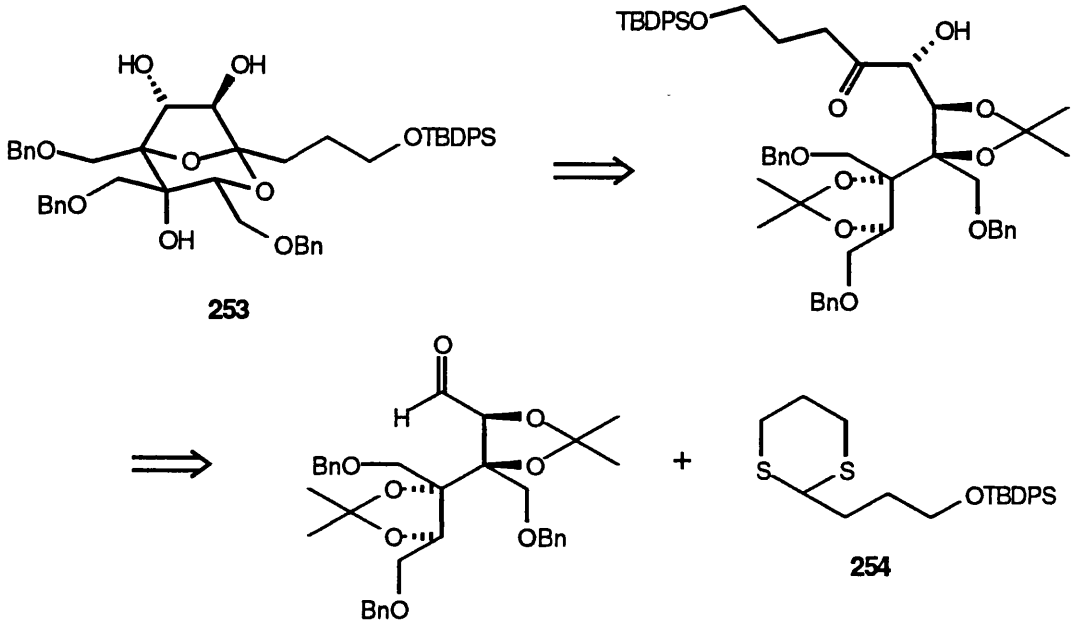
By this stage, we had decide to focus our efforts towards a total synthesis of the zaragozic acids, and these preliminary results directed at the novel triene route may be the subject of future investigations.

CHAPTER 3

Toward Zaragozic Acid D

3.1 Expansion of the route toward the zaragozic acids.

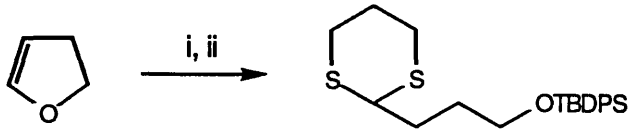
Initially, it seemed appealing to expand our core synthesis so as to incorporate a C1 substituent with appropriate functionality to allow access to any of the zaragozic acids. Our initial objective was to obtain the core **253** which we envisaged would arise by using the dithiane **254** instead of 2-methyl-1,3-dithiane (Scheme 117).



253 **218** **254**

Scheme 117

Thus, **254** was prepared according to Scheme **118**. Treatment of 2,3-dihydrofuran with 1,3-propanedithiol in the presence of $BF_3.OEt_2$ according to the literature procedure[124] afforded the 2-(3-hydroxypropyl)-1,3-dithiane, which following protection as the TBDPS ether gave the dithiane **254**.



254

Scheme 118

Reagents and conditions: i) 1,3-propanedithiol, $BF_3.OEt_2$ (cat), PhH, reflux, 3h, 51%; ii) TBDPSCl, imidazole, DMF, RT, 14h, 98%.

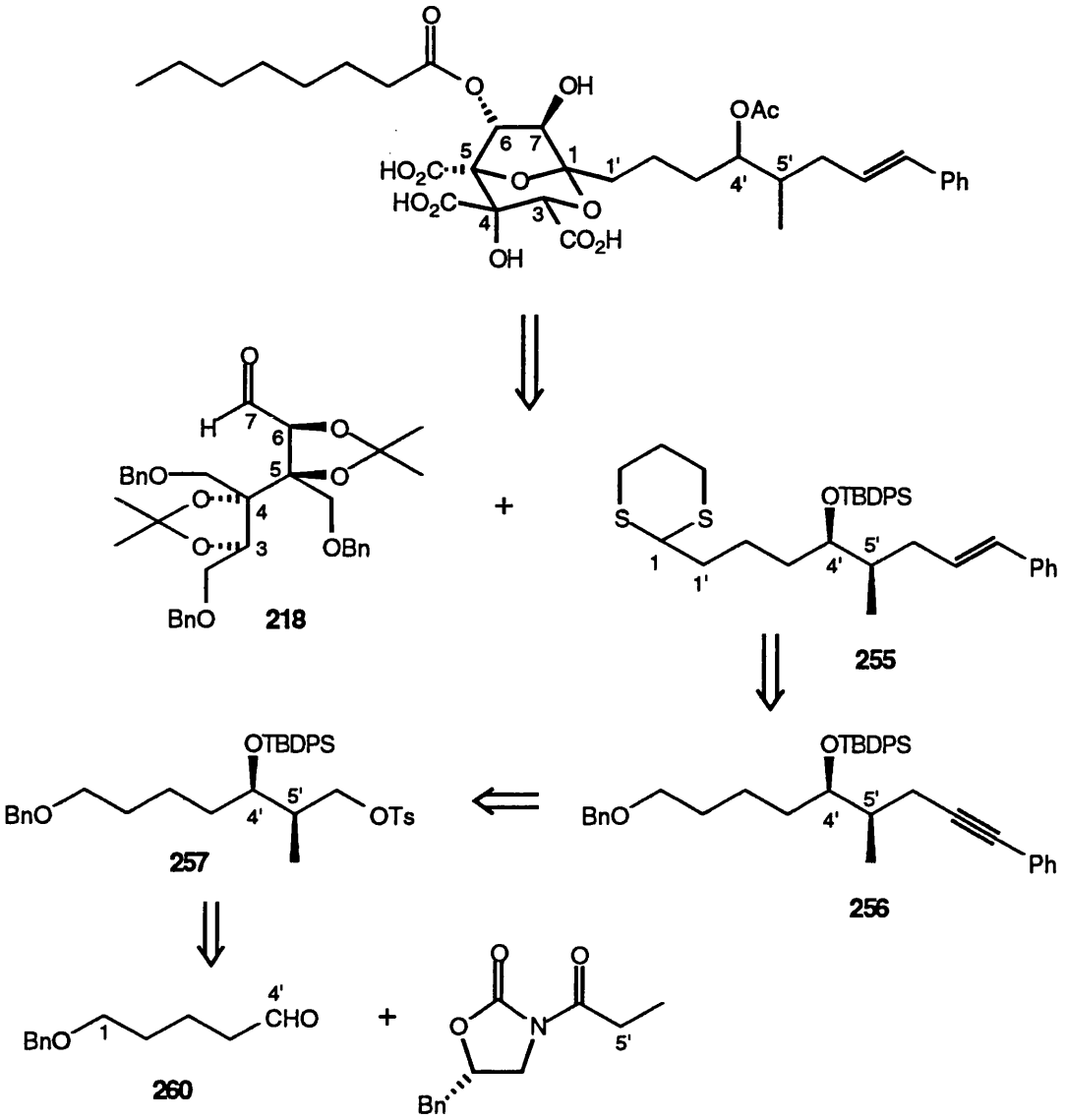
However, attempts to couple **254** with aldehyde **218** or even simply to anisaldehyde, under the same conditions as used earlier for 2-methyl-1,3-dithiane, resulted in no reaction. It was observed that treatment of **254** with ^{n}Buli rapidly led to the solution turning black. At that time this observation was not pursued, but it later became significant (*vide infra*).

By this time, we had decided to make zaragozic acid D our target for total synthesis, and hence immediately started work on a fully functionalised sidechain.

3.2 Retrosynthetic analysis of zaragozic acid D

Our approach to the total synthesis of zaragozic acid D involved the use of a 2-substituted 1,3-dithiane which would contain all the functionality of the natural product C1-sidechain. However, the stereochemistry of the C4' and C5' substituents in the C1 sidechain of zaragozic acid D are unknown.[8] Despite this, we thought it would be reasonable to assume they had the same relative configuration as all the other zaragozic acids with a C4' and C5' substituent. We would therefore require the dithiane **255** as our fully functionalised acyl anion equivalent (Scheme 119).

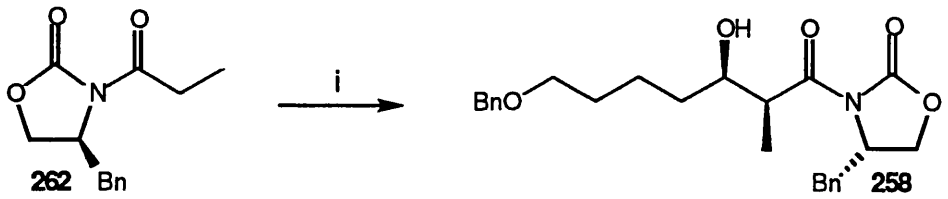
Model studies from our earlier work with simplified dithianes of type **254** (section 3.1, Scheme 117) indicated that the C4' substituent would require protection as the more robust TBDPS ether rather than the TBS ether in order for the protection to survive the Evans cyclisation conditions. We planned to use the Evans cyclisation conditions for construction of the bicyclic core since Nicolaou had reported the cleavage of the TBDPS group of his C1 sidechain under his 2%HCl/MeOH cyclisation conditions.[31d] Dithiane **255** would itself arise from dissolving metal reduction of the alkyne **256** which would allow simultaneous incorporation of the *E*-double bond and removal of the benzyl ether. The alkyne **256** could be installed *via* displacement of the tosylate **257** with lithium phenylacetylide.



Scheme 119

3.3 Synthesis of the C1 sidechain

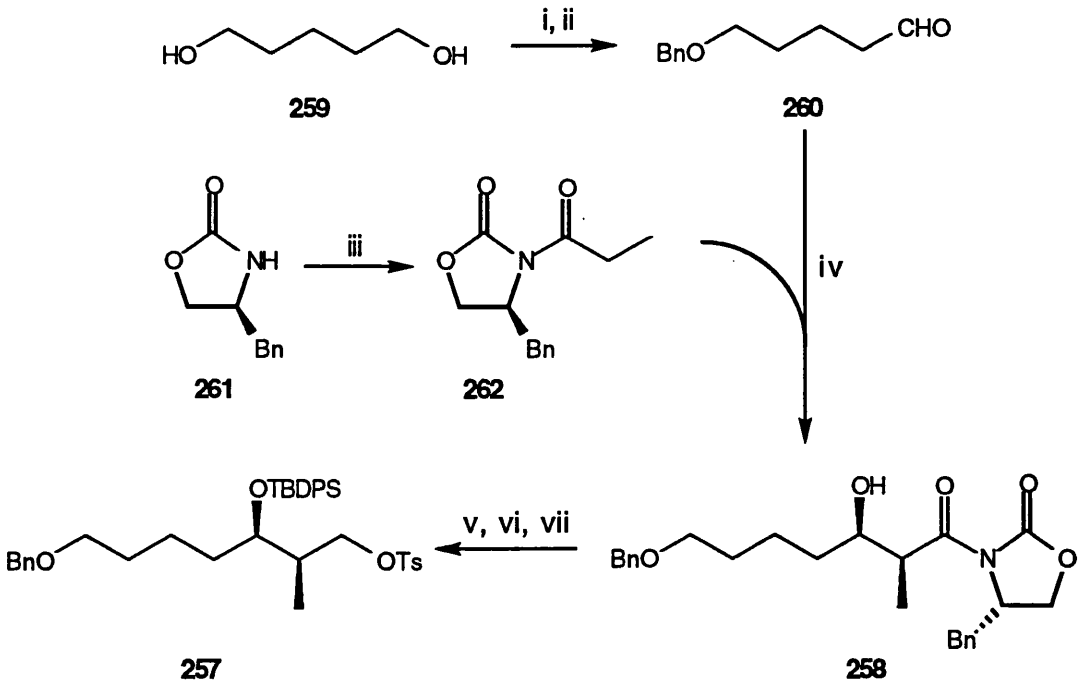
Carriera had reported the synthesis of the alcohol **258** during his synthesis of the C1 sidechain of zaragozic acid C,[32] *via* Evans aldol methodology (Scheme 120). We hoped that tosylate **257** could be obtained from **258**.



Scheme 120

Reagents and conditions: i) 9-BBNOTf, $^{i}Pr_2NEt$, CH_2Cl_2, -78°C then 5-(benzyloxy)pentanal, -78°C to RT over 12h, then H_2O_2/MeOH, 84%.

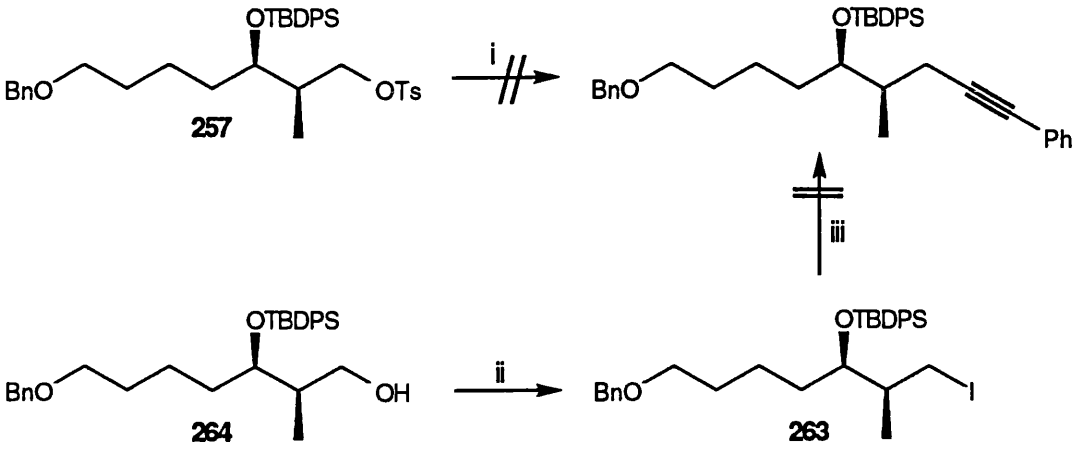
The synthesis of tosylate **257** is shown in Scheme 121. Thus, treatment of 1,5-pentane-diol **259** with NaH, benzyl bromide and catalytic Bu_4NI in DMF afforded the mono-benzyl protected alcohol in 45% yield, oxidation of which with PCC afforded aldehyde **260** (82%). Treatment of the Evans chiral auxiliary **261** with ^nBuLi followed by quenching with propionyl chloride afforded the oxazolidinone **262** in 91% yield. The subsequent aldol reaction giving alcohol **258** was modified not only in the conditions but also differring in the borane and base used to the procedure reported by Carriera.[32] Thus, addition of dibutylboron triflate (freshly prepared from tributyl borane and triflic acid) and triethylamine to oxazolidinone **262** at -78°C followed by addition of aldehyde **260** afforded the alcohol **258** in 81% yield as a single diastereoisomer, the data for which were identical to those reported by Carriera.[33] Our route from **258** now diverges from Carreira. Protection of **258** with TBDPSCl and imidazole in DMF, removal of the chiral auxiliary with $LiBH_4$ and MeOH in THF and then reaction of the resultant primary alcohol with *p*-toluenesulfonyl chloride in pyridine/CH_2Cl_2 afforded the tosylate **257**.



Scheme 121

Reagents and conditions: i) NaH, BnBr, $^nBu_4NI$ (cat), 0°C to RT, 2h, 45%; ii) PCC, CH_2Cl_2, 0.5h, 82%; iii) ^nBuLi, THF, -78°C, then propionyl chloride , -78°C to RT, 0.5h, 91%; iv) $^nBu_2BOTf$, Et_3N, CH_2Cl_2, -78°C then 0°C 45 mins, then **260**, -78°C to RT over 13h, then H_2O_2/MeOH, 0°C 0.5h then RT 1h, 81%; v) TBDPSCl, imidazole, DMF, 1d, 89%; vi) $LiBH_4$, MeOH, THF, 0°C to RT, 1.5h, 84%; vii) p-toluenesulfonyl chloride, pyridine, CH_2Cl_2, 1d, 89%.

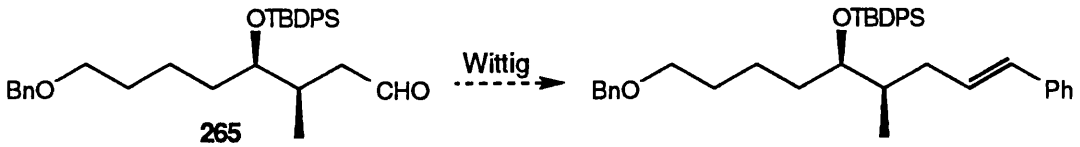
Unfortunately, attempts to displace the tosylate **257** with lithium phenylacetylide (freshly prepared from phenylacetylene and ^{n}BuLi) in THF at either RT or at reflux failed to give any reaction. For this reason, the iodide **263** was prepared (85% yield) by treatment of the alcohol **264** with triphenylphosphine, iodine and imidazole in toluene.[125] Again, no reaction was observed on heating **263** at reflux in THF with lithium phenylacetylide, even with the addition of LiCl or DMPU (Scheme 122).



Scheme 122

Reagents and conditions: i) lithium phenyl acetylide, THF, reflux; ii) PPh_3, I_2, imidazole, toluene, 14h, 85%; iii) lithium phenylacetylide, THF, DMPU or LiCl, reflux.

It was apparent that this approach did not offer a way forward, so it was decided to incorporate the *E*-double bond *via* Wittig olefination methodology (Scheme 123).

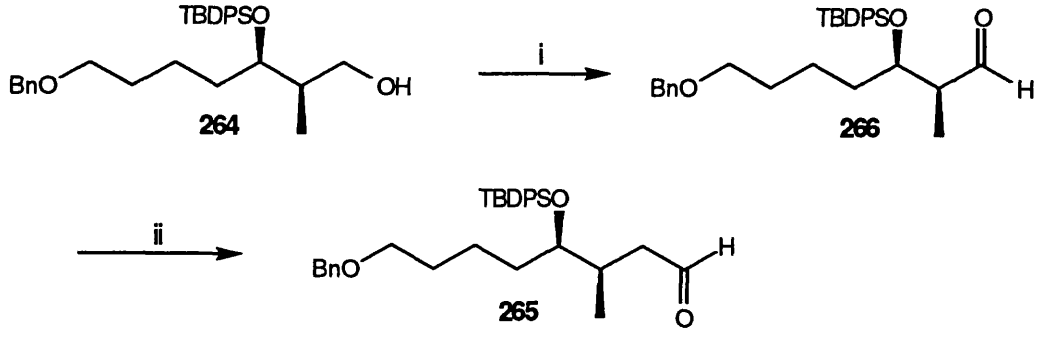


Scheme 123

This approach would require a one carbon homologation of the sidechain to provide the required aldehyde **265**, and Wittig methodology was also chosen for the homologation step since addition of methoxymethyl phosphoranes to aldehydes followed by hydrolysis of the resultant enol ether had been reported to be an efficient procedure for aldehyde homologation.[126] The preparation of **265** is shown in Scheme 124. Oxidation of alcohol **264**

with the Dess-Martin periodinane reagent afforded aldehyde **266** in 99% yield. The homologation of **266** to **265**, however, required some attention in order for the reaction to proceed reliably.

Initially, methoxymethyltriphenylphosphonium chloride was treated with PhLi followed by addition of **266** to the resulting suspension maintained at -50°C. The mixture was stirred at -30°C for 2h, then brought to RT and stirred for 5h. Addition of 60% perchloric acid then effected hydrolysis of the resultant enol ether **267** (Figure 22) *in situ.* After work-up and chromatography, several components were isolated. The ^{1}H and ^{13}C NMR of the product homologated aldehyde **265** also indicated the presence of the acetal **268** (Figure 22). This had presumably formed during the hydrolysis of **267** by reaction of the liberated aldehyde with MeOH in the presence of the perchloric acid. Compounds **265** and **268** co-ran on silica gel and could not be separated. The third component, (which by tlc appeared in the reaction *before* the addition of $HClO_4$), was identified as enal **269** (Figure 23), isolated in 34% yield.



Scheme 124

Reagents and conditions: i) Dess-Martin periodinane reagent, CH_2Cl_2, 20 mins, 99%; ii) methoxymethyltriphenylphosphonium chloride, PhLi, Et_2O, 15 mins, then **266** -50°C to -30°C, 2h, then RT for 5h, then $HClO_4$

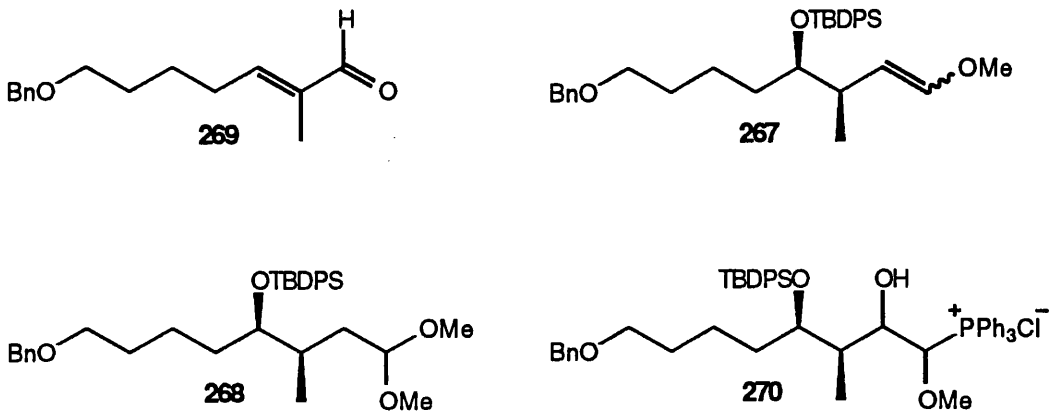
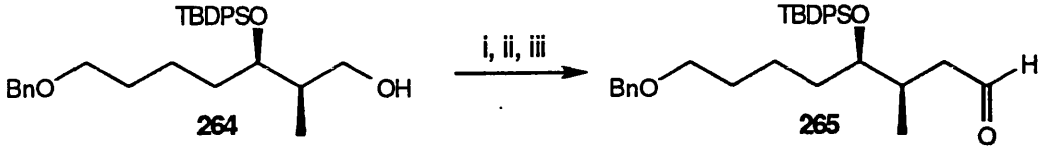


Figure 22: Intermediates and by-products obtained from aldehyde homologation

It was found that formation of the enal side-product **269**, (presumably arising from the Wittig reagent acting on **266** as a base, forming an anion α to the carbonyl, which then underwent elimination of the silyloxy group), could be completely avoided by simply pre-cooling the aldehyde **266** to -78°C prior to its addition to the Wittig reagent, also maintained at -78°C. When the reaction was left at -78°C, however, although tlc indicated the complete consumption of the starting aldehyde **266** after just 30 mins, work-up by quenching with water at -78°C, followed by addition of $HClO_4$, resulted in very low yields of **265**. Instead, an intractable oil which was insoluble in a wide range of organic solvents, was isolated. It was found that the isolated oil was the phosphonium salt **270** (Figure 22), a result of the elimination being suppressed at -78°C. However, simply treating isolated **270** with NaHMDS in benzene at RT effected the elimination to give quantitatively the enol ether **267** as a 1:1 stereoisomeric mixture (as observed by ^1H NMR of the crude reaction).

In addressing the undesired acetal formation during the $HClO_4$ hydrolysis step it was found that treatment of the crude isolated mixture of **265** and **268** with aqueous TFA in THF for 30 mins was sufficient to hydrolyse the majority of **268** to the aldehyde **265**, although it was never possible to obtain pure aldehyde from this reaction. Use of acetone and tosic acid to effect transketalisation gave inferior results leading to a 2:1 aldehyde **265**:ketal **268** ratio. The overall optimised conditions for the homologation are shown in Scheme 125. Thus, after the Dess-Martin oxidation, the aldehyde **266** was added to the Wittig reagent at -78°C (to avoid generation of the enal **269**), and once tlc indicated consumption of all the starting aldehyde **266**, the reaction mixture was allowed to warm to RT to effect completely the

elimination. Addition of perchloric acid followed by treatment of the crude isolated mixture of aldehyde **265** and ketal **268** with aqueous TFA in THF for 30 mins afforded the homologated aldehyde **265** in good overall yield (*ca.* 75%). No exact yield is quoted since it was never possible to fully hydrolyse the ketal **268**, and hence the near pure aldehyde **265** was used directly in subsequent steps.

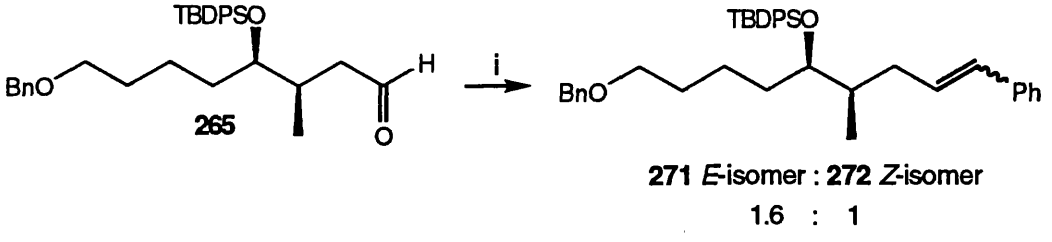


Scheme 125

Reagents and conditions: i) Dess-Martin periodinane reagent, CH_2Cl_2, 20 mins, 99%; ii) methoxymethyltriphenylphosphonium chloride, PhLi, Et_2O, 15 mins, then **266** -78°C, 35 mins then RT, 0.5h, then $HClO_4$; iii) THF/H_2O/TFA (20:5:1), 0.5h, *ca.* 75%.

With the desired homologated aldehyde **265** in hand, we could now turn our attention to the incorporation of the *E*-double bond. This was initially investigated with benzyltriphenylphosphonium bromide, as although an E/Z mixture was expected with this Wittig reagent, it was envisaged that subsequent isomerisation to the thermodynamically favoured *E*-isomer could be readily effected.

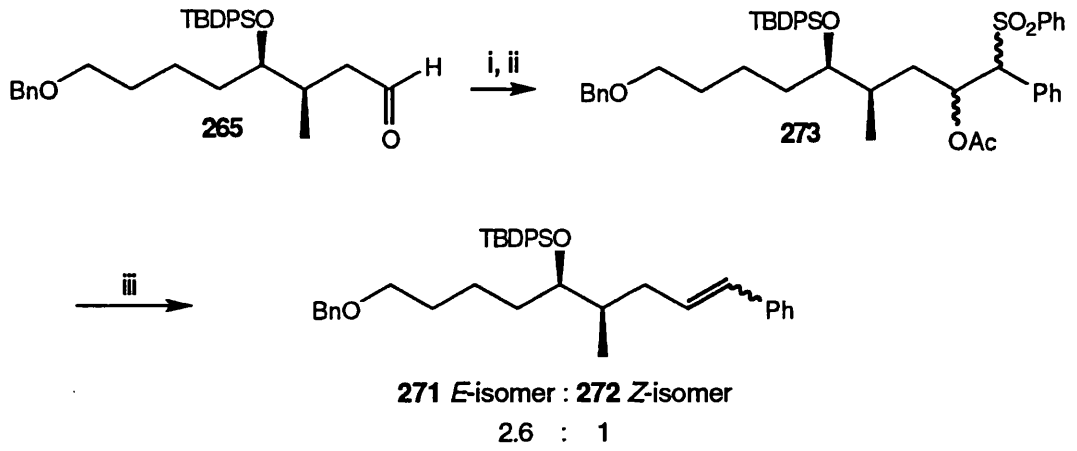
Thus, when aldehyde **265** was added to a suspension of the lithium salt of benzyltriphenylphosphonium bromide, the corresponding olefins **271** and **272** were obtained as an inseparable 1.6:1 mixture of the *E*:*Z* isomers (as determined by analysis of the crude ^1H NMR) (Scheme 126). Unfortunately, all attempts to isomerise the *Z*-to the *E*-double bond with catalytic iodine and/or hυ failed.



Scheme 126

Reagents and conditions: i) benzyltriphenylphosphonium bromide, PhLi, Et_2O, 0.5h, RT, then **265**, 97%.

In light of the failure to isomerise the *Z*- to the *E*-olefin, a more selective olefination approach was required. Julia olefination methodology offered one such approach since it is is highly *E*-selective. Thus, treatment of **265** with the anion derived from benzylphenyl sulfone followed by *in situ* quenching with acetyl chloride afforded the crude β-acetoxy sulfones **273** as a mixture of diastereoisomers. However, better yields were realised by acylation of the isolated β-hydroxy sulfones with acetic anhydride in pyridine. Reductive elimination was effected by use of the recently reported system[127] employing Mg powder in the presence of catalytic amounts of $HgCl_2$ in EtOH to afford the olefins **271** and **272** as a 2.6:1 *E*:*Z* mixture of isomers in an overall yield of 56% (Scheme 127). This ratio was disappointingly low since Julia olefination methodology is usually reliable in terms of the reactions high *E*-selectivity.

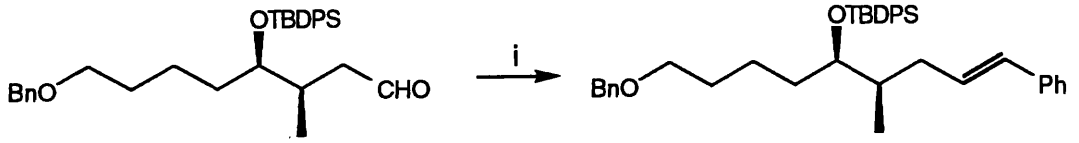


271 *E*-isomer : **272** *Z*-isomer
2.6 : 1

Scheme 127

Reagents and conditions: i) benzylphenyl sulfone, ^{n}BuLi, THF, 0.5h, RT, then **265**; ii) acetic anhydride, pyridine; iii) Mg powder, $HgCl_2$ (cat), EtOH, 56% overall.

The stereoselective synthesis of the *E*-olefin **271** was ultimately achieved by means of a recently reported[129] modification of the Wadsworth-Emmons olefination, employing crown ethers. Thus, addition of a mixture of aldehyde **265** and diethylbenzylphosphonate to a slurry of NaH in THF containing catalytic amounts of 15-crown-5 exclusively afforded the desired *E*-olefin **271** (Scheme 128). The *Z*-isomer was undetectable in the 500 MHz ^{1}H NMR spectrum.



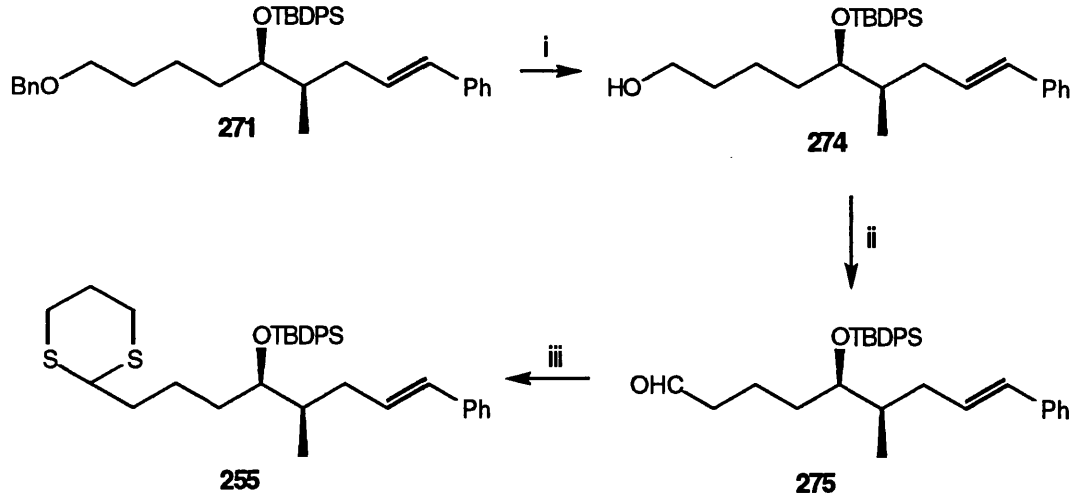
265 271

Scheme 128

Reagents and conditions: i) diethylbenzylphosphonate, NaH, 15-Crown-5 (cat), THF, 0°C to RT, 1.5h, 70%.

With **271** now in hand, the remaining steps of the sidechain synthesis were completed, according to Scheme 129.

Attempted debenzylation of **271** (in the presence of the double bond) with Na in liquid ammonia and EtOH at -78°C failed to give any of the alcohol, but gratifyingly, use of $BCl_3.SMe_2$ in CH_2Cl_2 afforded alcohol **274** in 95% yield.[60] Oxidation of **274** to the aldehyde **275** with the Dess-Martin periodinane reagent, under the Schreiber modification[130] (addition of up to one equivalent of water to the reaction, *vide infra*), followed by protection with 1,3-propane-dithiol in the presence of catalytic $BF_3.OEt_2$ furnished the 1,3-dithiane **255**.[132]



Scheme 129

Reagents and conditions: i) $BCl_3 \cdot SMe_2$, CH_2Cl_2, RT, 1.5h, 95%; ii) Dess-Martin periodinane reagent, CH_2Cl_2, then H_2O (1 eq), 15 mins, 94%; iii) 1,3-propanedithiol, 20 mol% $BF_3 \cdot OEt_2$, CH_2Cl_2, 12h, 100%.

With the 1,3-dithiane **255** now serving as our fully functionalised C1 sidechain, we now required the aldehyde **218** in order to investigate the coupling to **255**.

While earlier we had obtained aldehyde **218** *via* Swern oxidation, during the synthesis of the C1 sidechain, a new batch of the Dess-Martin periodinane (DMP) reagent had been prepared.[129, 131] In light of the findings by Schreiber and co-workers that addition of up to one equivalent of water had a greatly beneficial effect on the oxidation of alcohols, we re-investigated the use of the DMP reagent for the oxidation of the bis-acetonide alcohol **212** to the corresponding aldehyde **218**. This modification now gave the desired aldehyde **218**, but the yields varied considerably (60%-90%) due to the impracticability of adding the same precise amount of water each time for the scale these oxidations were carried out.

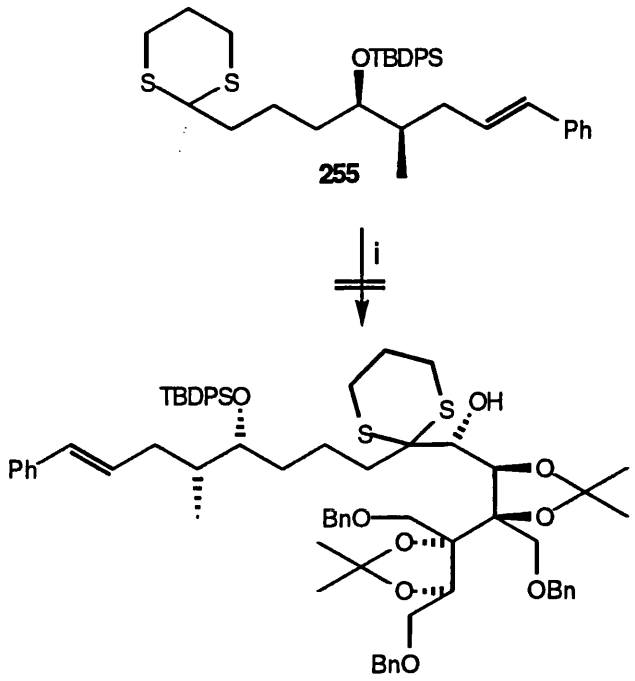
Nonetheless, the greater convenience of this procedure over the previously employed Swern oxidation made these the conditions of choice for obtaining aldehyde **218**.

3.4 Attempted coupling of the C1 sidechain 255 to aldehyde 218.

With the dithiane **255** in hand, the final C-C bond forming reaction could be investigated which would install the entire carbon backbone of zaragozic acid D.

The standard conditions for anion formation of 2-substituted 1,3-dithianes require treatment of the dithiane with ^{n}BuLi at -40°C which is then held at -25°C for 1.5h to complete deprotonation.[113a] The solutions remain colourless unless the 2-substituent is an aryl group.

However, treatment of dithiane **255** with ^{n}BuLi at -40°C resulted in a deep red solution on warming to -25°C. After 1.75h at -25°C, the mixture was cooled to -78°C prior to addition of aldehyde **218**. However, on cooling **255** to -78°C, the solution turned pale yellow and it was noticed that the stirrer bar had turned black, much in the same way as it would for a dissolving metal reduction in liquid ammonia, possibly indicating that electron transfer processes were in operation. Addition of the aldehyde to the mixture resulted in no reaction and after work-up the sidechain **255** and aldehyde **218** were recovered fully intact (Scheme 130).



Scheme 130

Reagents and conditions: i) ^{n}BuLi, THF, -40°C to -25°C, 1.75h, then -78°C, **218**.

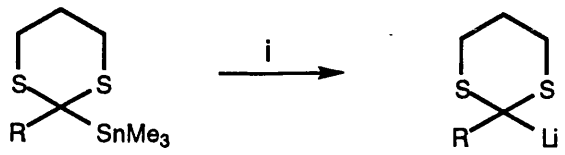
Many repeats of the reaction always gave the same result, and some interesting observations were made when temperature changes were made during the anion formation.

Thus, addition of ^{n}BuLi at -78°C resulted in a very pale yellow solution, which turned deep orange on warming through the temperature range of -30°C to -24°C. Re-cooling the solution to -37°C resulted in a yellow solution, which on warming again to -30°C did not turn back to the deep orange colour, but on the contrary, turned an even paler yellow. As always, the stirrer bar had turned black. Although the sidechain was usually recovered in high yield, the ^{1}H NMR of the recovered sidechain indicated the presence of a small amount of another compound. It was not known if a dianion of some description was being formed, which might involve deprotonation of a phenyl ring as well as the dithiane. It was also speculated that the ^{n}BuLi might have been adding to the styrene double-bond, which might account for the small amounts of suspected benzylic signals observed in the ^{1}H NMR of recovered **255**.

To this end, a deuterium incorporation study was undertaken. The dithiane **255** was treated with ^{n}BuLi at -40°C and then held at -25°C for 1.5h. The resultant red solution was quenched at -50°C with D_2O. It was found that use of a substantial excess of ^{n}BuLi (*ca.* 4

equivalents) was required to fully incorporate deuterium at the 2-position of the dithiane. However, due to poor resolution of the ^1H nmr spectrum, it was not possible to acertain whether deuterium had been incorporated elsewhere in the molecule.

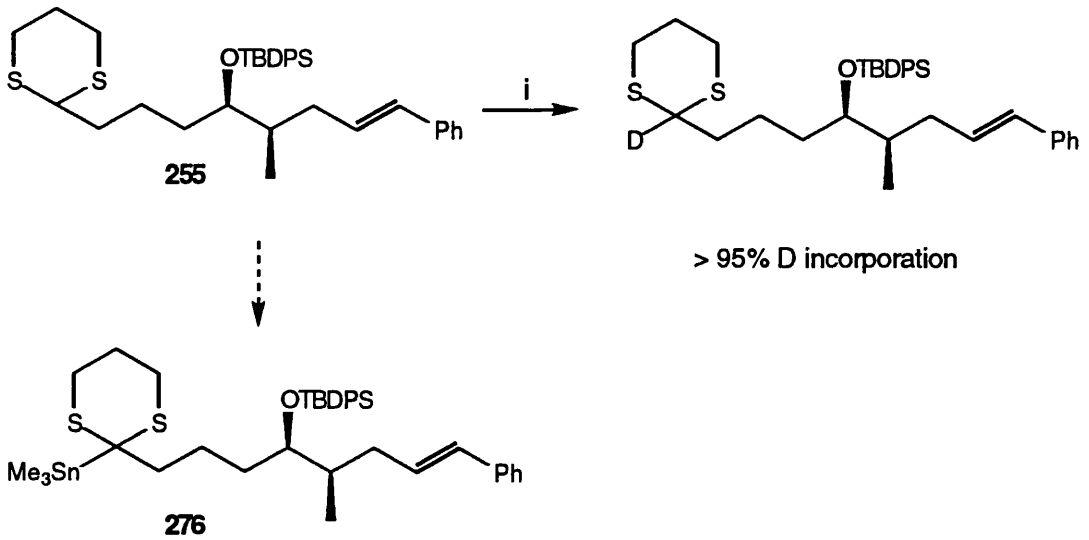
Since direct deprotonation seemed problematic, it was thought that an approach aimed at lithiation of a 2-halo- or 2-stannyl-1,3-dithiane might alleviate the problem. Indeed, it was reported[132] that 2-trimethylstannyl-1,3-dithianes undergo spontaneous transmetallation on addition of ^{n}BuLi at -100°C (Scheme 131).



Scheme 131

Reagents and conditions: i) ^{n}BuLi, THF, -100°C, 5 secs.

We knew we could get complete deuterium incorporation on D_2O quenching if a large excess of ^{n}BuLi was employed, and we therefore hoped that quenching with Me_3SnCl under the same conditions would generate the 2-trimethylstannyl-1,3-dithiane **276** (Scheme 132).



Scheme 132

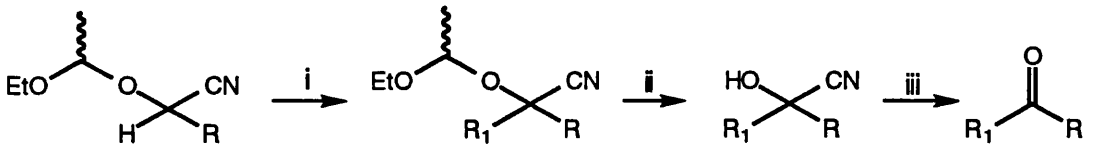
Reagents and conditions: i) ^{n}BuLi (*ca.* 4 eq), THF, -40°C to -25°C, 1.5h, then -50°C, D_2O.

Unfortunately, the trimethylstannyl group could not be incorporated using this approach.

Given the inherant problems encountered in generating 2-lithio-1,3-dithianes, we thought at this stage it would be prudent to investigate the use of a different acyl anion equivalent which could be generated under milder conditions.

3.5 Use of protected cyanohydrins as our acyl anion equivalent.

Due to the metallation problems with our 1,3-dithiane **255** we had decided to employ a different acyl anion equivalent which might prove somewhat easier to metallate. Stork reported ethoxyethyl protected cyanohydrins to be useful acyl anion equivalents.[133] The ethoxyethyl protecting group served to stabilise the resultant α-cyano carbanion, thus allowing for the use of aliphatic aldehydes as well as aromatic ones as cyanohydrin precursors. The deprotonation was reported to be effected under the mild conditions of LDA in THF/HMPA at -78°C after 5 mins. The ketone could be regenerated by hydrolysis of the ethoxyethyl protecting group with 5% H_2SO_4 followed by treatment of the resultant cyanohydrin with base (Scheme 133).



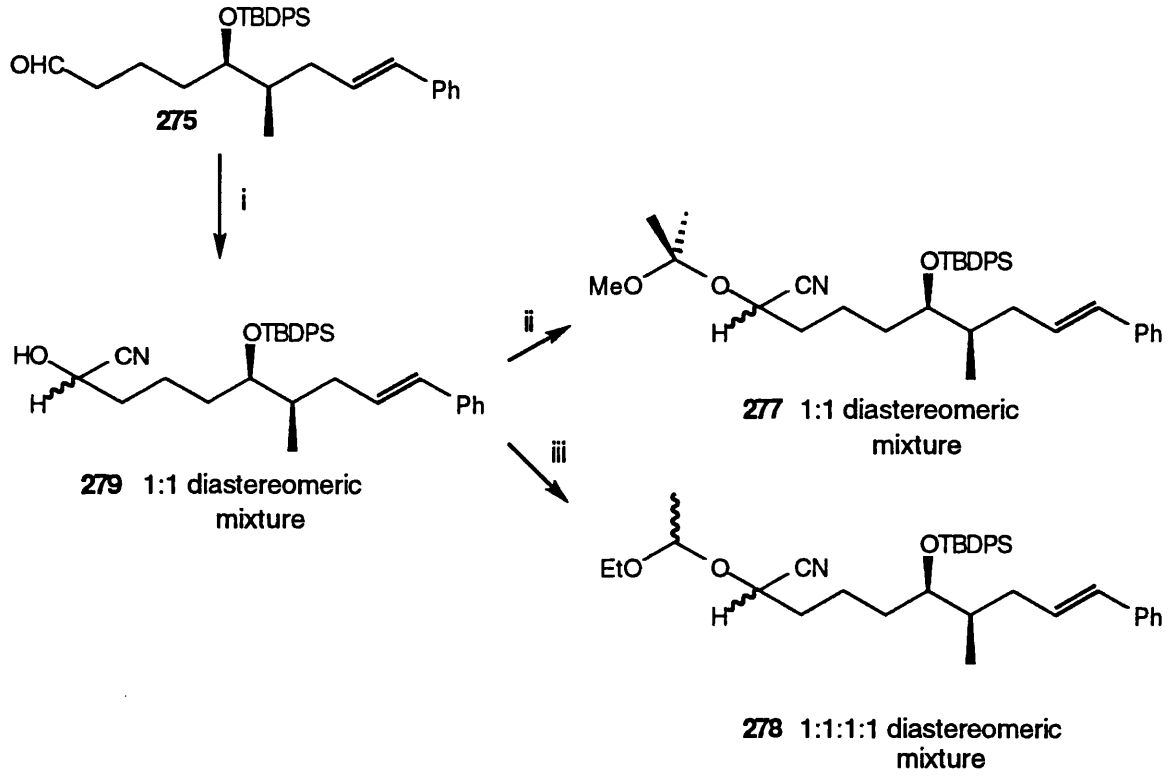
Scheme 133

Reagents and conditions: i) LDA, THF/HMPA, -78°C, 5 min, then R_1X; ii) 5% H_2SO_4/MeOH, iii) NaOH or Et_3N/acetone.

However, an additional problem in using the ethoxyethyl cyanohydrin would be the generation of several other diastereoisomers arising from an additional two chiral centres. Therefore, in the hope of reducing by half the number of diastereoisomers that the addition reaction would inevitably generate, (a new chiral centre is generated at C7 in the addition process), the 1-methyl-1-methoxyethyl protected cyanohydrin **277** was prepared as well as the ethoxyethyl protected cyanohydrin **278** (Scheme 134). Thus, treatment of the previously

obtained aldehyde **275** with TMS-cyanide in CH_2Cl_2 in the presence of cat. ZnI_2,[134] followed by addition of THF, TFA and H_2O afforded the cyanohydrins **279** as a 1:1 diastereoisomeric mixture. Treatment of **279** with 2-methoxypropene and catalytic *p*-TsOH afforded the 1-methyl-1-methoxyethyl protected cyanohydrins **277** as a 1:1 mixture of diastereoisomers.

Treatment of **279** with ethyl vinyl ether and catalytic *p*-TsOH resulted in a multi-component mixture. It was found that ethyl vinyl ether and *p*-TsOH reacted together exothermically giving rise to a brown polymeric mixture. Use of PPTS in place of *p*-TsOH remedied this to afford the ethoxyethyl protected cyanohydrins **278** as a 1:1:1:1 mixture of diastereoisomers.

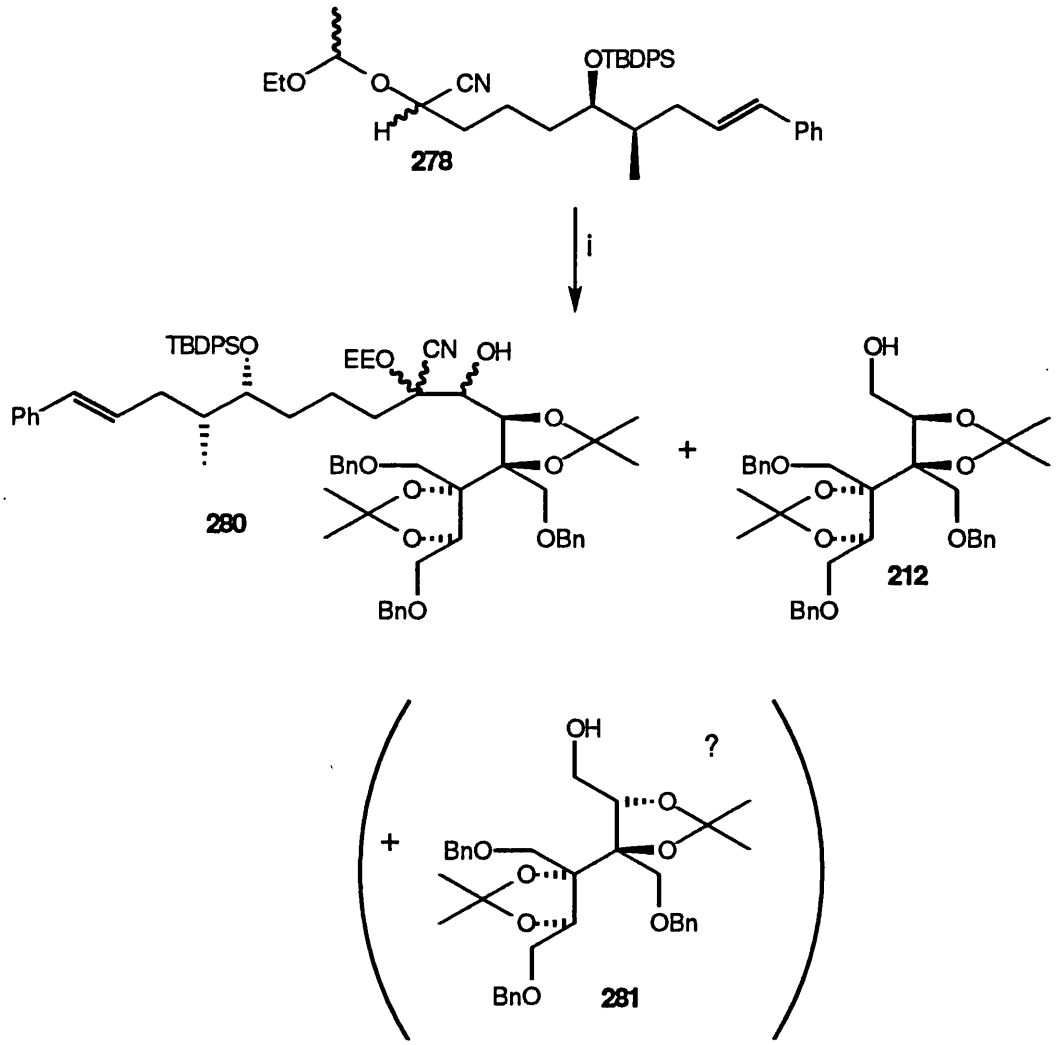


Scheme 134

Reagents and conditions: i) TMSCN, ZnI_2 (cat), CH_2Cl_2, 0°C to RT, 0.5h, then TFA/THF/H_2O (1:1:1), 10 mins, 88%; ii) 2-methoxypropene, *p*-TsOH (cat), 5 mins, 82%; iii) ethyl vinyl ether, PPTS (cat), CH_2Cl_2, RT, 15h, 84%.

Attempted coupling of either **277** or **278** under the Stork conditions,[133] (except with the omission of HMPA), to aldehyde **218** resulted in no reacton. When HMPA was employed in the coupling of **278** to **218** aldehyde, small amounts of what is believed to be

coupled product **280** (~10%) were isolated (Scheme 135). The ^1H NMR of the purified components indicated a grossly indistinguishable diastereomeric mixture, but the presence of the characteristic olefinic protons and the butyl signal of the TBDPS group of the sidechain, and the acetonides from the aldehyde fragment, suggested that the observed products were a result of the coupling. The unreacted sidechain was recovered. However, aldehyde **218** had disappeared and an inseparable by-product, that appeared by TLC and ^1H NMR to be the bis-acetonide alcohol **212** contaminated with a very similar compound, (thought to be the epimer **281**), was formed. A likely explanation for this observation is that the LDA had not deprotonated **278** to any significant extent and had acted as a hydride transfer agent.

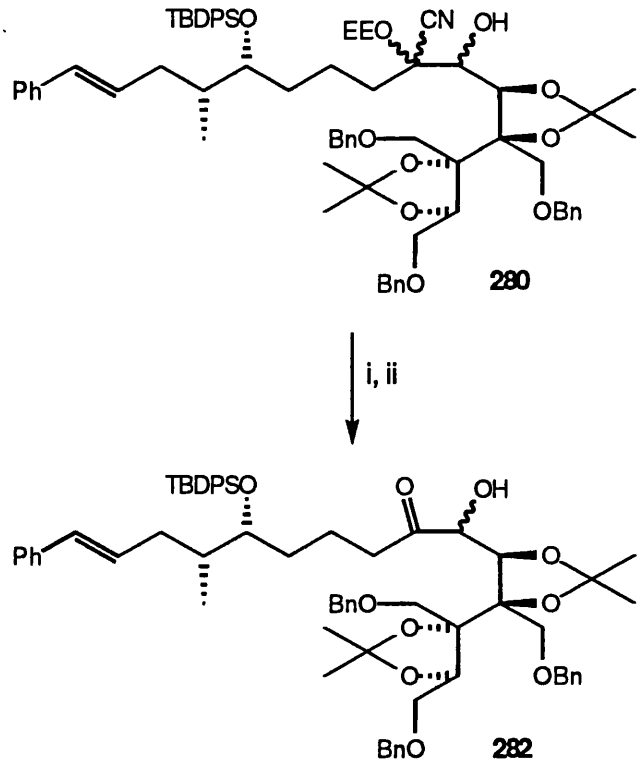


Scheme 135

Reagents and conditions: i) LDA, THF/HMPA, -78°C, 5 mins, then **218**, 1h.

It was thought that use of the more bulky NaHMDS base might alleviate reduction of **218** since it is unable to act as a hydride transfer agent. Use of NaHMDS did indeed eliminate the hydride transfer process, but offered no improvement in the yield of coupled products. Again, the C1 sidechain was recovered intact.

Unfortunately, no conditions could be found to effect the coupling with these protected cyanohydrins to ever produce more than 10% of coupled products. The small amounts of coupled products, though gross diastereomeric mixtures, were nonetheless converted to the ketone **282** (Scheme 136), but no full characterisation was possible and the structures are only supported by ^{1}H NMR, IR (confirming the presence of the ketone) and Mass Spec.



Scheme 136

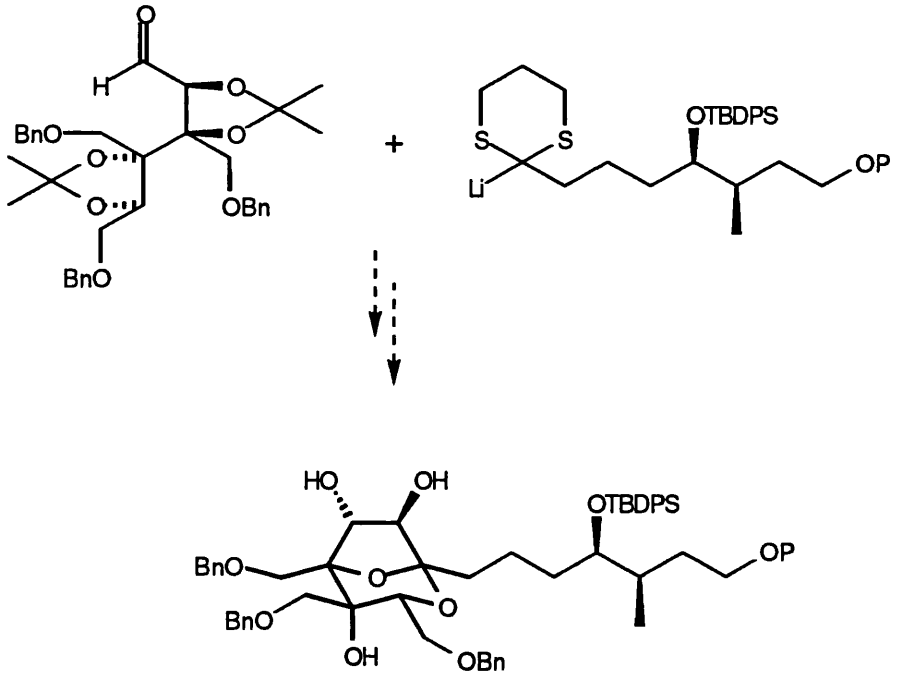
Reagents and conditions: i) 5% H_2SO_4/MeOH, RT, 1h; ii) Et_3 N/acetone, RT, 4.5h.

The lack of success with the protected cyanohydrin **278** as acyl anion equivalents was disappointing and it was unclear why the reaction was always so low yielding. It was not clear what the way forward would be with this approach since there seemed little scope for modification of the conditions. However, for the previously tried 1,3-dithiane **255**, it was thought side-reactions, due to the double bond in conjugation with the phenyl group present

in **255**, might in some way be responsible for the failure of the reaction to couple to the aldehyde. It was therefore decided to reinvestigate the use of dithianes as the acyl anion equivalent, but without the double-bond functionality, with a view to incorporating it at a later stage in the synthesis.

3.6 The 1,3-dithiane: revisited.

As mentioned above, we thought that if the double bond was responsible for the difficulties encountered in the metallation of dithiane **255**, then replacement with a group that could allow for its later incorporation should permit continuation of the synthesis without too much deviation from our original synthetic plan. We decided that a protected alcohol functionality at the terminus of the chain would be suitable to carry out the same synthetic procedures once the addition product had been cyclised to the desired 2,8-dioxabicyclo[3.2.1]octane ring system (Scheme 137).

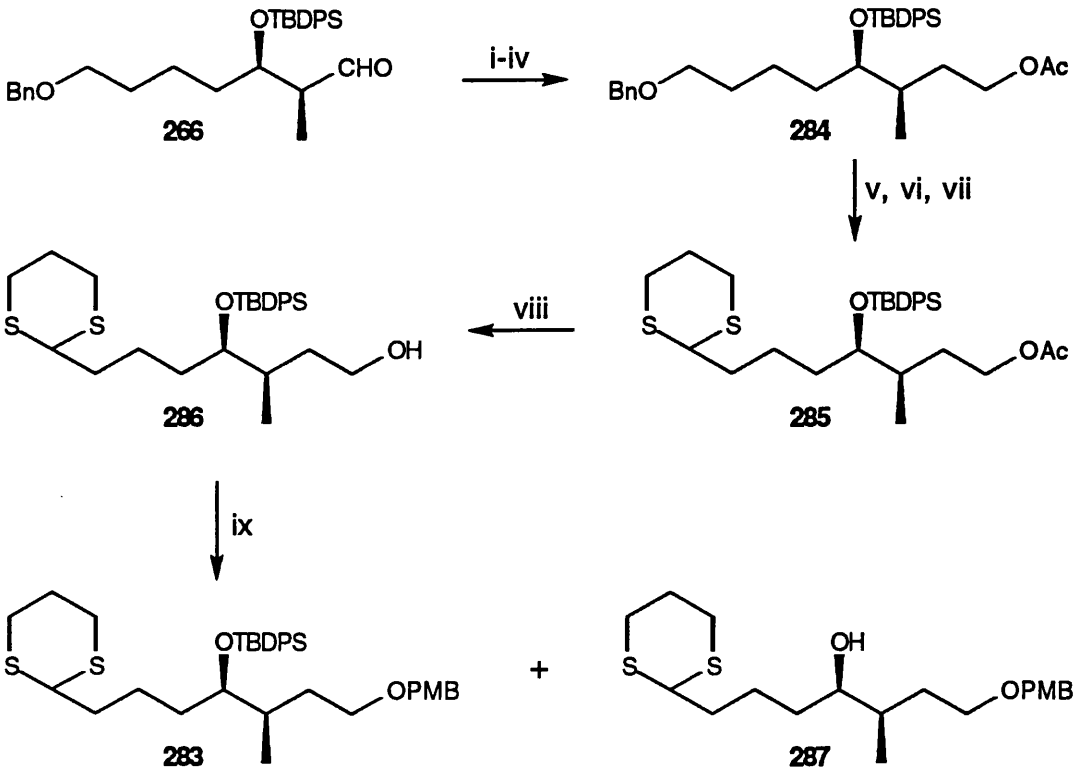


Scheme 137

The primary alcohol protecting group was chosen on the basis of: 1) compatibility with dithiane metallation conditions, 2) being robust enough to withstand the ketalisation

conditions, and 3) to allow for its selective removal in the presence of the TBDPS- and benzyl ethers. This somewhat limited the choice, but the *p*-methoxybenzyl ether fulfilled all three requirements. For this reason, the dithiane **283** was chosen and prepared according to Scheme 138.

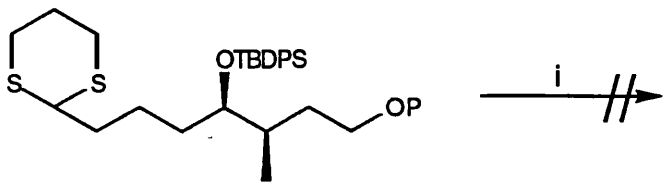
Thus, homologation of aldehyde **266** as previously detailed (Scheme 125), followed by reduction with $NaBH_4$ in MeOH to the corressponding alcohol and subsequent protection with acetic anhydride in pyridine/CH_2Cl_2 gave the acetate **284**. Debenzylation of **284** with $BCl_3.SMe_2$ in CH_2Cl_2, Dess-Martin periodinane oxidation followed by protection with 1,3-propanedithiol and catalytic $BF_3{\cdot}OEt_2$ afforded the dithiane **285**. Removal of the acetate protecting group with K_2CO_3 in MeOH gave the alcohol **286** in 98% yield. However, treatment of **286** with PMBCl, NaH and catalytic Bu_4NI in DMF led to a mixture of products including a meagre 10% **283** which we were unable to isolate in pure form along with 16% recovered starting material. It was found that one of the main products formed was alcohol **287** where the TBDPS group had been removed. Omitting the catalytic Bu_4NI resulted in almost exclusive formation of **287**. It was later discovered that it had already been reported that use of NaH in HMPA was an extremely efficient method for the deprotection of TBDPS ethers,[135] and this would appear to account for the formation of **287**. Attempts to protect the primary hydroxyl of **286** with *p*-methoxybenzyltrichloroacetimidate using 0.3 mol% TfOH generated a mixture of products. The *p*-methoxybenzyltrichloroacetimidate reagent had been reported as being extremely sensitive to the amount of TfOH employed.[136] 10 mol% TfOH was reported to be sufficient to cause its rapid and complete destruction. It had been suggested that use of catalytic CSA instead of TfOH, in CH_2Cl_2, although giving very slow reaction rates, proved a superior system.[136] Protection of **286** under these conditions was indeed slow, and also generated a mixture of components. Again, a low yield of **283** was obtained and **283** could not be effectively purified.



Scheme 138

Reagents and conditions: i) methoxymethyltriphenylphosphonium chloride, PhLi, Et_2O, 15 mins, then **266** -78°C, 35 mins then RT, 0.5h, then $HClO_4$; ii) THF/H_2O/TFA (20:5:1), 0.5h, *ca.* 75%.iii) $NaBH_4$, MeOH, RT, 1h, %; iv) acetic anhydride, pyridine, CH_2Cl_2, 15h, 97%; v) $BCl_3{\cdot}SMe_2$, CH_2Cl_2, RT, 20 mins, 92%; vi) Dess-Martin periodinane reagent, CH_2Cl_2, then H_2O (1 eq), 35 mins, 92%; vii) 1,3-propanedithiol, 20 mol% $BF_3{\cdot}OEt_2$, CH_2Cl_2, 16h, 87%; viii) K_2CO_3, MeOH, RT, 1h, 98%; ix) PMBCl, NaH, $^nBu_4NI$ (cat), DMF, RT, 10% **283**.

Despite this, the coupling reaction of **283** to aldehyde **219** was investigated under the standard anion formation conditions of ^{n}BuLi at -25°C for 1.5h. However, no reaction was observed, even in the presence of added HMPA (Scheme 139). The bis-silyl ether **288** (prepared by silylation of **286** with TBDMSCl and imidazole in DMF) also failed to couple in similar conditions.



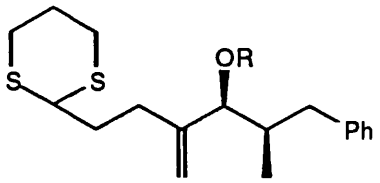
283 P=PMB
288 P=TBS

Scheme 139

Reagents and conditions: i) ^{n}BuLi, THF, -40°C to -25°C, 1.5h, then -78°C, **218**.

However, by this stage we felt there was enough experimental evidence to hypothesise that the TBDPS group was a culprit in these attempted metallation reactions. In the attempted coupling of the simple dithiane **254** (see 3.1) the reaction turned black under the metallation conditions, and failed to give any product. The protection of **286** with NaH and PMBCl led to the removal of the TBDPS group, and indeed was a reported procedure for its deprotection, indicating a possible incompatibility of this group towards anions/bases. During the Nicolaou synthesis of zaragozic acid A, several sidechains such as ours were employed.[31d] All added in reasonable yield with just little over one equivalent of the sidechain being required. However, when R=TBDPS, a significant excess of the sidechain was necessary with respect to the aldehyde fragment, but when R=DTBMS, 1.1 equivalents were sufficient, again possibly indicating a problem specific to the TBDPS group (Figure 23).

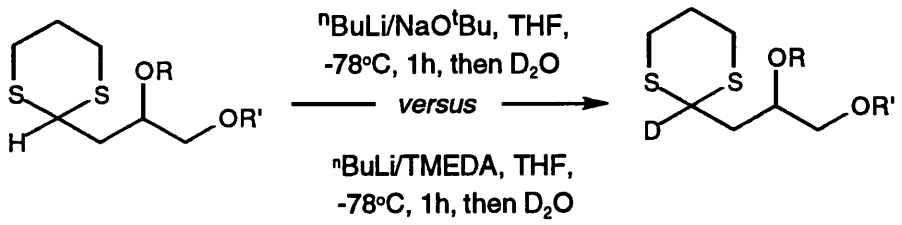
It would seem the phenyl groups on silicon might be the cause of the problem. A literature survey highlighted several problematic metallations of dithianes containing the TBDPS group, although no comment ever suggested the TBDPS group might be to blame. Lipshutz reported[137] that the problems of these metallations could be overcome by use of NaO^{t}Bu and ^{n}BuLi which after 1h at -78°C, gave greatly increased yields of product (Scheme 140).

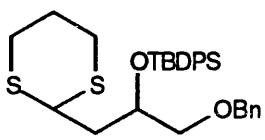


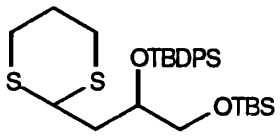
R= PMB, TBDPS, DTBMS

Figure 23

The rationale behind this combination of reagents were several fold. Firstly, the intrinsically stronger base expected from NaO^{t}Bu and ^{n}BuLi might be of a lower aggregation state. Also, although dithianes lithiate with a strong preference for the equatorial site, the sodio analogue might have different stereoelectronic/steric demands, which might in turn lead to differing reactivity. Once metalated, the sodio analogue should exhibit greater reactivity over the lithiated dithiane, due in part to less favourable driving forces for oxygen-sodium chelation.



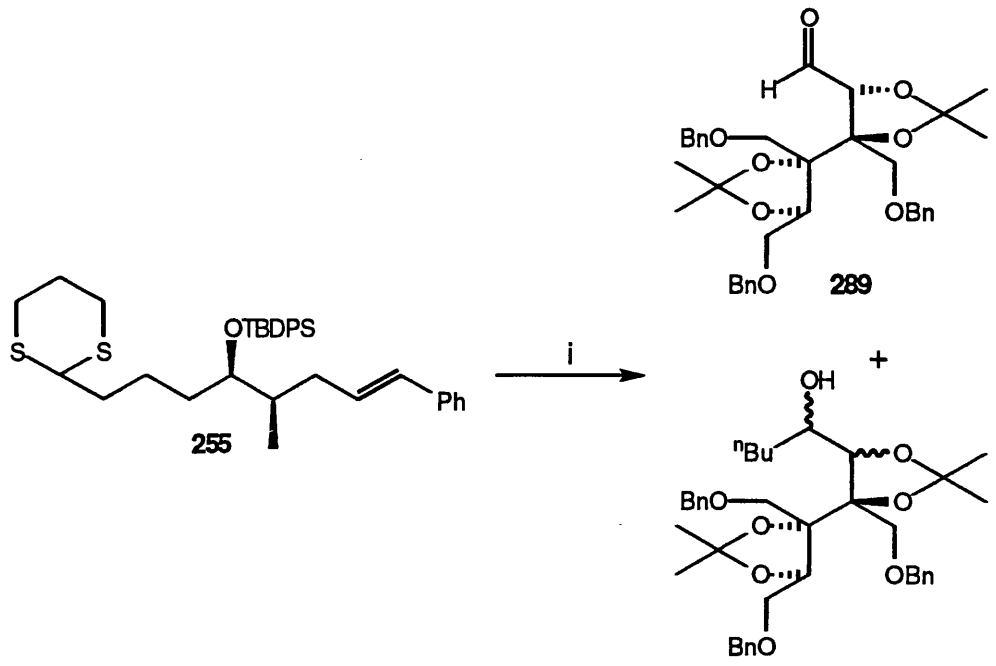




	%D	%D
nBuLi/NaOtBu:	***>99***	***>95***
nBuLi/TMEDA:	<20	<25

Scheme 140

Therefore the coupling of our original fully functionalised C1 sidechain dithiane **255** to aldehyde **218** was re-investigated under the Lipshutz conditions as follows: A suspension of NaO^{t}Bu and ^{n}BuLi were stirred in hexanes at 0°C for 1h, then at RT for 1h, then pre-cooled to -78°C. The dithiane **255** was then added. This mixture was stirred for a further hour at -78°C before the addition of aldehyde **218** (Scheme 141). Unfortunately, no coupled product was observed, and the dithiane **255** was recovered fully intact. However, none of aldehyde **218** was recovered. Instead, the epimerised aldehyde **289** and a mixture of products which appeared to have arisen from addition of the butyl group to aldehyde **218** and/or **289** were isolated.



Scheme 141

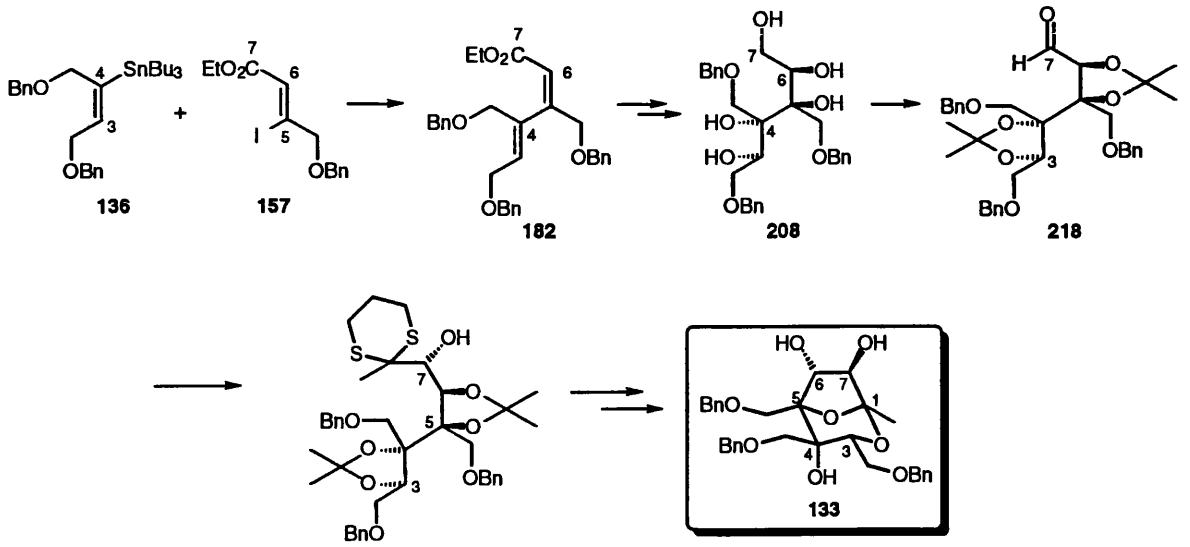
Reagents and conditions: i) ^{n}BuLi/NaO^{t}Bu, THF, -78°C, 1h, then **218**.

This last reaction marks the present state of affairs with this route toward zaragozic acid D. The synthesis of zaragozic acid D has so far been thwarted by our inability to couple the C1 sidechain to the key aldehyde **218**. Many months of frustrated effort have been directed solely at achieving this coupling. Although it has been very disappointing not to have achieved the total synthesis, it is hoped that the following section might offer some possible way forward for future workers.

3.7 Conclusions and further work.

The novel and challenging structure of the zaragozic acids, along with their potent biological activity, have made these compounds a major target for the international community of synthetic organic chemists. Our efforts in this field have led us to report[138] the concise synthesis of the model core **133**, *via* the key aldehyde **218** (Scheme 142). A Stille cross-coupling between the stereodefined alkenes **136** and **157** afforded the stereochemically pure 1,3-diene **182** in excellent yield. A novel variation of the Sharpless asymmetric dihydroxylation (AD) was used to control stereochemistry at four contiguous stereocentres

of the core to give the pentaol **208** (78% ee, diastereomeric ratio >9:1). This is one of the first examples of enantioselective *exhaustive* dihydroxylation of a 1,3-diene. This use of Stille coupling methodology in conjunction with the Sharpless AD provides a powerful new approach to polyol synthesis. Addition of 2-lithio-2-methyl-1,3-dithiane to **218** to introduce the C1-side chain, followed by deprotection and ketalisation afforded the model bicyclic core **133**.



Scheme 142:Summary of our model core synthesis

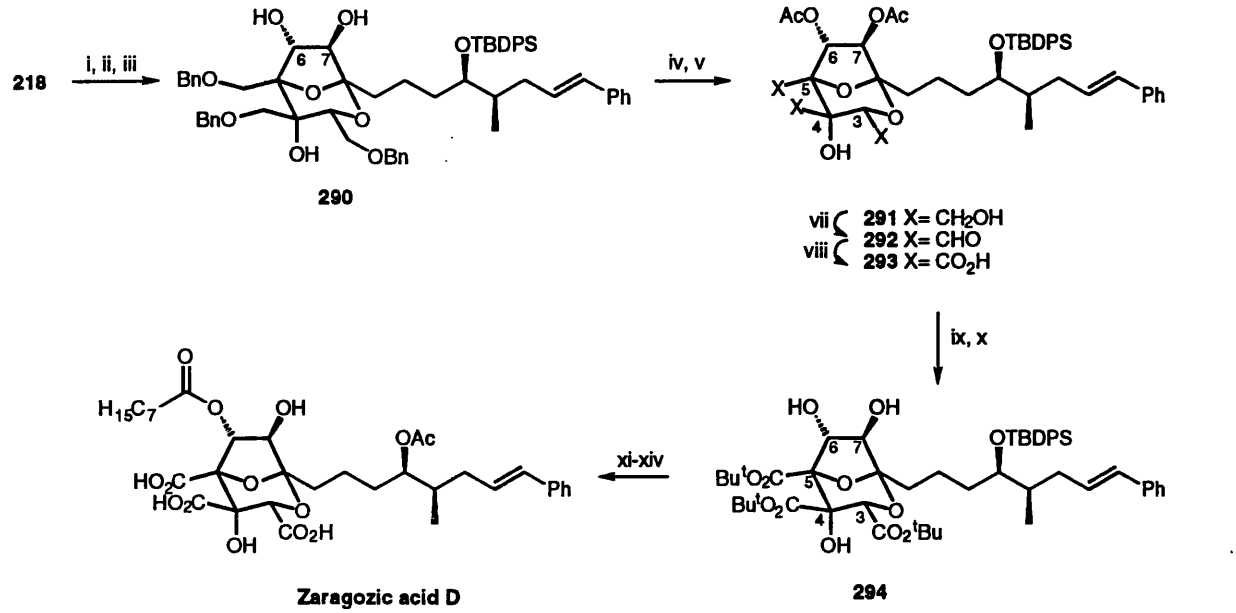
To illustrate our approach beyond the synthesis of a model core, we chose zaragozic acid D as our target for total synthesis. We have accomplished the synthesis of the C1 side chain **255** of zaragozic acid D in enantiomerically pure form, with absolute and relative stereochemistry being controlled by Evans aldol methodology. Efforts to couple this sidechain, and several other sidechain derivatives, to the key aldehyde **218**, have failed as a result of metallation problems.

However, a large range of options are still available. For example, Danishefsky[139] reported that a mixture of KO^{t}Bu and ^{n}BuLi (the so-called LICKOR base) at -78°C required only 20 minutes to completely effect the metallation of a complex 2-substituted-1,3-dithiane containing silyl ether groups. In addition, the literature shows that metallation of dithianes containing the TBDPS protecting group can, for the majority cases, be effected by use of *tert*-butyl lithium. Therefore, it is thought that employing either of these conditions should

lead to the coupling of **255** to aldehyde **218**, and a proposed route for the completion of the synthesis of zaragozic acid D is shown in Scheme 143.

Addition of dithiane **255** under one of the above sets of conditions, is expected to generate a mixture of stereoisomers at C7, as was the case in our model study. It is hoped that the desired diastereomer will again be readily separable. Following removal of the dithiane group, acid-promoted ketalisation will afford the desired 2,8-dioxabicyclo[3.2.1]octane core **290** now containing the fully functionalised C1 sidechain. Acetylation of the C6 and C7 hydroxyls of **290** and simultaneous removal of the three benzyloxy protecting groups will set the stage for an unprecedented triple oxidation of the triol **291** to the triacid **293** *via* the trialdehyde **292**. A possible problem inherent in the oxidation of any 1,4-diol is cyclisation of an intermediate hydroxy aldehyde to the lactol and subsequent oxidation to the lactone, effectively preventing complete oxidation of one of the original alcohols. However, use of the Swern oxidation ($(COCl)_2$ / DMSO) should overcome this problem since the aldehyde is only generated *after* addition of triethylamine. Since all three alcohols would be activated prior to this, an *in situ* protection of the alcohols would be effected, thereby inhibiting potential cyclisation to a lactol. Indeed, there is precedent for use of the Swern oxidation to convert 1,4-diols to the corresponding dialdehydes,[140] and it is hoped that this transformation can be applied to our more complex triple oxidation of triol **291**. Carreira has recently shown that a trialdehyde similar to **292** (prepared by sequential oxidations) can be oxidised to the acid with buffered $NaClO_2$ and converted to the corresponding tris *tert*-butyl ester.[32] It is therefore hoped that application of these steps to our trialdehyde **292** should give the corresponding tris *tert*-butyl ester **294**.

All subsequent remaining steps of the synthesis will follow recent precedent by Carreira. Selective Boc protection of the C7-OH will leave the C6-OH free to allow esterification at the C6 hydroxyl.[32] Fluoride-mediated removal of the TBDPS group, acetylation of the side-chain hydroxyl, and simultaneous removal of the Boc- and ^tBu esters with TFA will complete the first total synthesis of zaragozic acid D.



Scheme 143

Reagents and conditions: i) metallated **255**; ii) $Hg(ClO_4)_2$, $CaCO_3$, $THF:H_2O$; iii) H^+; iv) Ac_2O; v) Debenzylation; vi) Swern oxidation; vii) $NaClO_2$; viii) ^tBu esterification; ix) Acetate removal (K_2CO_3, MeOH); x) $(Boc)_2O$, 4-pyrrolidinopyridine, CH_2Cl_2; xi) $C_7H_{15}COCl$; xii) F^-; xiii) Ac_2O; xiv) TFA.

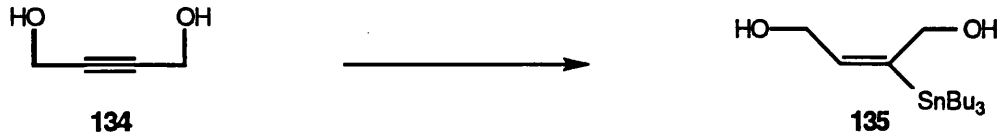
CHAPTER 4

Experimental

General Procedures

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on either Jeol GX-270, Jeol EX-400, Jeol FX-270, Bruker AM 250, Bruker AM 400, or Bruker DRX 500 machines or an Hitachi Perkin-Elmer R-24B 60 MHz NMR spectrometer, using residual protic solvent ($CHCl_3$, δ_H=7.26 ppm) or $CDCl_3$ (δ_C=77.0 ppm, t) as internal reference. Coupling constants are measured in Hertz and have been read directly from the peak printout, and hence are quoted uncorrected. The multiplicities in ^{13}C spectra were determined by DEPT experiments. Infra-red spectra were run on a Perkin-Elmer 1605 FT-IR machine and were run from 4000-600 cm^{-1}. Mass spectra were recorded under conditions stated for that particular compound, using a VG-7070B, VG Micromass 70E, VG Biotech Quattro II, VG ZAB-E or VG Autospec; Microanalyses were performed at either the microanalytical laboratories of the University of Bath or Nottingham. Optical rotations were measured using a JASCO DIP-370 digital polarimeter. Column chromatography was performed on Merck Kieselgel 60 (230-400 mesh) unless otherwise stated. Diethyl ether and tetrahydrofuran solvents were distilled from sodium-benzophenone ketyl; toluene from sodium and dimethylformamide, dichloromethane and *N*-methylpyrollidinone from calcium hydride. Petrol refers to petroleum ether b.p. 60-80°C which was distilled prior to use. Other solvents and reagents were purified by standard procedures as necessary.[141] Analytical thin layer chromatography was performed using pre-coated glass-backed plates (Merck Kieselgel 60 F_{254}) and visualised by ultra-violet light and/or acidic ceric ammonium molybdate, polyphosphoric molybdic acid or potassium permanganate as appropriate.

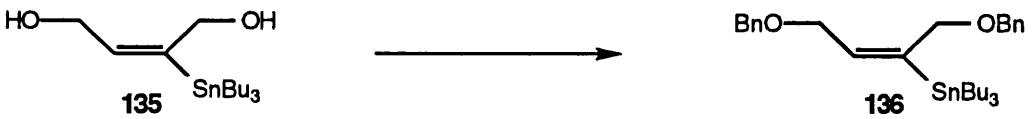
Preparation (*E*)-2-(tri-n-butylstannyl)-2-butene-1,4-diol 135



134 135

To a stirred solution of 2-but-2-yne-1,4-diol **134** (4.30 g, 50 mmol) in dry THF (150 ml) containing $Pd(PPh_3)_2Cl_2$ (700 mg, 1 mmol, 2 mol%) was added tributyltin hydride (14.6 ml, 55 mmol) dropwise over 6 mins. After 5 mins, more tributyltin hydride (1.3 ml, 5 mmol) was added in one portion. The reaction immediately darkened and was concentrated *in vacuo*. The residual brown oil was purified by FCC (20%-100% EtOAc/Petrol) to give the title compound **135** (16.90g, 90%) as a yellow oil. The data obtained were consistent with the literature;[142] δ_H (270 MHz, $CDCl_3$) 5.80 (1H, tt, *J* 6 Hz, 2 Hz, $^3J_{SnH}$ 68Hz), 4.40 (2H, s, $^3J_{SnH}$ 36 Hz), 4.21 (2H, d, *J* 6 Hz), 1.70 (2H, bs), 1.60-1.20 (18H, m), 0.90 (9H, t, J 7 Hz).

Preparation of (*E*)-1,4-Bis-(benzyloxy)-2-(tri-n-butylstannyl)-2-butene 136

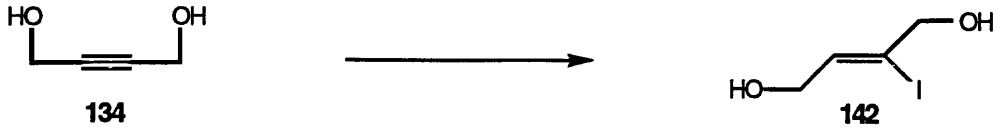


135 136

To a stirred solution of diol **135** (3.04 g, 8.05 mmol) in dry DMF (30 ml) under N_2 was added NaH (445 mg, 18.53 mmol) followed by tetrabutylammonium iodide (152 mg, 0.40 mmol, 5 mol%) and benzyl bromide (2.10 ml, 17.70 mmol). The reaction was stirred in the dark for 2.5h, then filtered (fluorosil) washing through with Et_2O. The Et_2O layer was separated, and the DMF extracted with Et_2O (x3). The ethereal layers were combined, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual yellow liquid was purified by FCC (0-6% Et_2O/petrol) to give the title compound **136** (3.2g, 71%) as a clear oil, ν_{max}(film) 3030, 2954, 2923, 2852, 1496, 1454, 1358, 1091, 1028, 735, and 697 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.31-7.17 (10H, m, Ph), 5.71-5.66 (1H, m, C*H*=), 4.42 (2H, s, PhCH_2), 4.40 (2H, s, PhCH_2), 4.09 (2H, d, *J* 1.3 Hz, CH_2), 3.96 (2H, d, *J* 5.7 Hz, CH_2), 1.48-1.13 (18H, m, CH_2), 0.90 (9H, t, *J* 7.0 Hz, CH_3); δ_C(100 MHz, $CDCl_3$) 148.2, 138.3,

135.0, 128.4, 128.2, 127.9, 127.8, 127.6, 127.5, 72.7, 72.2, 71.7, 67.3, 29.1, 27.4, 13.7, 10.2; m/z (EI) 501 (M^+-C_4H_9), 451 (M^+-$PhCH_2O$), 291 ($^{120}Sn(C_4H_9)_3$), 91 ($PhCH_2$); found: C, 64.9; H, 8.37. $C_{30}H_{46}O_2Sn$ requires C, 64.7; H, 8.32%.

Preparation of (Z)-2-Iodo-2-butene-1,4-diol 142



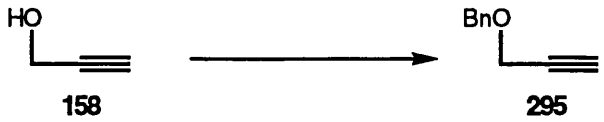
To a stirred slurry of $LiAlH_4$ (3.10 g, 81.6 mmol) in dry ether (100 ml) under N_2 was added 2-butyne-1,4-diol **134** (4.30 g, 50 mmol) in dry THF (170 ml+ 30 ml washing) dropwise over 25 mins *via* cannula. The mixture was heated at reflux for 1h 20 mins and then the excess $LiAlH_4$ was quenched with dry EtOAc (50 ml) at 0°C. The reaction was cooled to -78°C and quenched with iodine (48.5 g, 200 mmol) in dry THF (150 ml) and ether (100 ml) *via* cannula over 8 mins. The mixture was stirred at -78°C for 25 mins, then diluted with EtOAc (100 ml) and poured onto basic saturated aqueous sodium thiosulfate solution (200 ml). The aqueous phase was saturated with solid NaCl, and the organic layer was separated. The aqueous layer was extracted with EtOAc (4 x 100 ml), the organics combined, then washed with saturated aqueous sodium thiosulfate (3 x 100 ml), dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual orange oil was pre-adsorbed onto silica gel (silica-methanol) prior to purification by FCC (40-80% EtOAc/petrol) to give the title compound **142** (6.63 g, 62%) as a yellow oil, ν_{max}(film) 3303, 3183, 1648, 1233, 1079, 1033, 978, and 959 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.31-6.20 (1H, m, C*H*=), 4.36-4.20 (4H, m, CH_2), 2.50 (1H, br, O*H*); δ_C(100 MHz, $CDCl_3$) 133.5, 107.6, 71.2 , 66.7 ; m/z (EI) 214 (M^+), 196, 183, 168, 127; observed: M^+, 213.9489. $C_4H_7IO_2$ requires M^+, 213.9491.

Preparation of 4-(*tert*-butyldimethylsiloxy)-2-butyn-1-ol 149

134 149

To a cooled (0°C), stirred solution of 2-butyne-1,4-diol **134** (0.50 g, 5.81 mmol) in dry DMF (15 ml) under N_2 was added NaH (153 mg, 6.10 mmol). The mixture was stirred at RT for 1h and then TBDMSCl (0.92 g, 6.10 mmol) was added at 0°C. The reaction was stirred at 0°C for 3.5h, then at RT for 16h before the addition of saturated aqueous NH_4Cl (10 ml). The mixture was extracted with Et_2O (3 x 30ml) and the extracts combined and washed with saturated aqueous NH_4Cl (3 x 20ml) and saturated aqueous brine (3 x 20ml), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by FCC (5-30% Et_2O/petrol) to give the title compound **149** (497 mg, 42%) as a colourless liquid; the data obtained were consistent with the literature;[142] δ_H(400 MHz, $CDCl_3$) 4.34 (2H, t, *J* 1.8 Hz, CH_2O), 4.28 (2H, t, *J* 1.8 Hz, CH_2O), 2.20 (1H, bs, O*H*), 0.90 (9H, s, ^tBu), 0.11 (6 H, s, Me_2Si).

Preparation of 3-(Benzyloxy)propyne 295

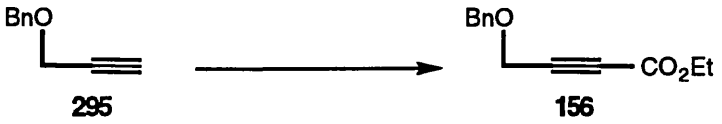


158 295

To a cooled (0°C), stirred solution of propargyl alcohol **158** (10 ml, 171 mmol) in dry DMF (100 ml) was added NaH (4.93 g, 205 mmol) portionwise, followed by tetrabutylammonium iodide (3.17 g, 8.58 mmol) and benzyl bromide (22.4 ml, 188 mmol). The reaction was allowed to warm to RT and stirred in the dark for 24h before the addtion of saturated aqueous NH_4Cl. The mixture was extracted with Et_2O (x3). The ethereal layers were combined and washed with 2M NaOH (x2), water (x2), and saturated aqueous brine (x2), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual orange oil was purified by FCC (0-5% Et_2O/petrol) to give the title compound **295** (22.79 g, 91%) as a

yellow liquid; the data obtained were consistent with reported literature;[143] ν_{max}(film) 3292, 3064, 3031, 2856, 2116, 1724, 1496, 1454, 1355, 1075, 1028, 936, 741 and 698 cm^{-1}; δ_H (60 MHz, $CDCl_3$) 7.4-7.2 (5H, m, Ph), 4.6-4.4 (2H, m, $PhCH_2OCH_2$), 4.2-4.0 (2H, m, $PhCH_2OCH_2$), 2.5-2.3 (1H, m, C≡C*H*).

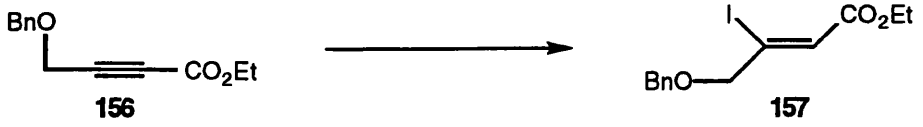
Preparation of Ethyl 4-(benzyloxy)-2-butynoate 156



295 156

To a cooled (-78°C), stirred solution of **295** (11.57g, 79.2 mmol) in dry THF (400 ml) was added ^{n}butyl lithium (36.4 ml, 2.5 M solution in hexanes, 91.10 mmol) over 25 mins under N_2. After 1h, ethyl chloroformate (15.13 ml, 158.4 mmol) was added dropwise over 12 mins. The temperature was raised to 0°C and the mixture stirred for 50 mins before quenching with saturated aqueous $NaHCO_3$ (250 ml). The mixture was allowed to warm to RT and stirred for a further 50 mins before partitioning between water (150 ml) and CH_2Cl_2 (200 ml). The aqueous layer was extracted with CH_2Cl_2 (2 x 100ml) and the organics combined then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by FCC (10% Et_2O/petrol) to give the title compound **156** (14.5 g, 84%) as a yellow liquid; the data obtained were consistent with the literature;[144] δ_H(60 MHz, $CDCl_3$) 7.35-7.2 (5H, m, Ph), 4.5 (2H, m, $PhCH_2OCH_2$), 4.12 (2H, m, $PhCH_2OCH_2$), 4.11 (2H, q, *J* 7.0 Hz, $CO_2CH_2CH_3$), 1.16 (3H, t, *J* 7.0 Hz, $CO_2CH_2CH_3$).

Preparation of (*Z*)-Ethyl 4-(benzyloxy)-3-iodo-2-butenoate 157

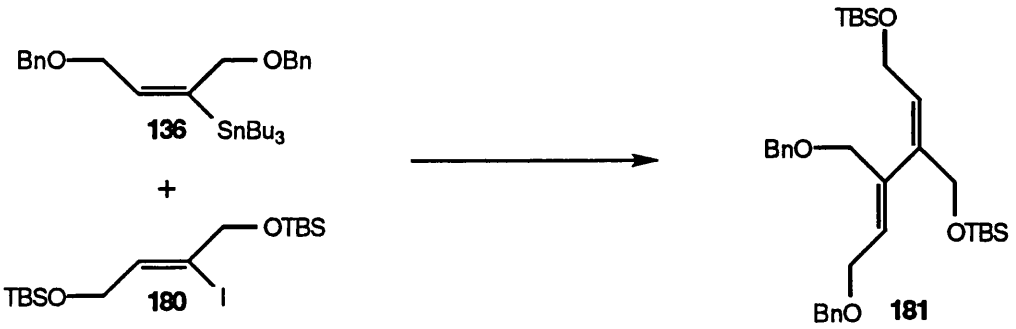


156 157

To a stirred solution of **156** (9.22 g, 42.30 mmol) in glacial acetic acid (40 ml) was added LiI (6.23 g, 46.53 mmol). The reaction was heated at 70°C for 1.5h and then allowed to cool

to RT. The mixture was evaporated *in vacuo* (azeotroping with toluene) and the residue was taken up in Et_2O and filtered to remove the inorganics. Additional Et_2O was added and washed with saturated aqueous $NaHCO_3$ (x5). The aqueous layers were combined and back extracted with Et_2O (x3), and the ethereal layers combined and washed with saturated aqueous sodium thiosulfate (x3), then water (x2) and saturated aqueous brine (x3). The organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by FCC (10% Et_2O/petrol) to give the title compound **157** (14.67 g, 100%) as a pale yellow liquid, ν_{max}(film) 3030, 2980, 2865, 1726, 1632, 1496, 1454, 1365, 1286, 1177, 1106, 1051, 857, 738 and 698 cm^{-1}; δ_H(400 MHz, $CDCl_3$) 7.30-7.16 (5H, m, Ph), 6.73 (1H, t, *J* 1.8 Hz, C*H*=), 4.48 (2H, s, PhCH_2OCH_2), 4.16 (2H, d, *J* 2.1 Hz, PhCH_2OCH_2), 4.15 (2H, q, *J* 7.0 Hz, $CO_2CH_2CH_3$), 1.22 (3H, t, *J* 7.0 Hz, $CO_2CH_2CH_3$); δ_C(100 MHz, $CDCl_3$) 164.3, 137.0, 128.4, 127.9, 127.6, 123.7, 115.8, 78.9, 72.4, 60.6, 14.1; m/z (EI) 346 (M^+), 301, 254, 240, 226, 209, 198, 189, 143, 127, 113, 91, 77; found: C, 45.5; H, 4.6. $C_{13}H_{15}IO_3$ requires C, 45.1; H, 4.4%).

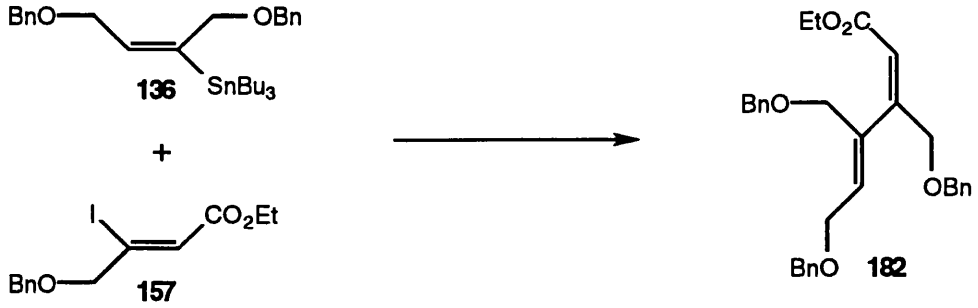
Preparation of (*Z*,*E*)-6-benzyloxy-4-(benzyloxymethyl)-1-(*tert*-butyldimethylsilyloxy)-3-(*tert*-butyldimethylsilyloxymethyl)-2,4-hexadiene 181



Vinyl iodide **180** (80 mg, 0.18 mmol) was dissolved in dry DMF (1 ml). The solution was degassed with N_2 for 10 mins prior to the addition of $ZnCl_2$ (49 mg, 0.36 mmol) followed by *tri*-(2-furyl)-phosphine (1.7 mg, 0.07 μmol) and $Pd_2(dba)_3$ (1.6 mg, 0.04 μmol Pd). The solution was stirred for 10 mins until the purple colour had discharged before the addition of the vinyl stannane **136** (110 mg, 0.20 mmol) neat, rinsing in with DMF. The mixture was heated at 88°C for 24h and then allowed to cool to RT before the addition of 10% NH_4OH

(1 ml). After 5 mins the mixture was extracted with Et_2O (x3) and the extracts were combined and washed with water (x2), saturated aqueous brine (x2), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by FCC (0-15% Et_2O/petrol) to give the title compound **181** (28 mg, 27%) as a clear oil, ν_{max}(film) 3055, 3029, 2953, 2929, 2885, 2857, 1496, 1471, 1386, 1362, 1254, 1070, 1004, 939, 836, 780, 736, 697 and 670 cm^{-1}; δ_H(270 MHz, $CDCl_3$) 7.33-7.17 (10H, m, Ph), 5.65 (1H, t, *J* 6.4 Hz with finer coupling, C*H*=), 5.55 (1H, t, *J* 6.6 Hz with finer coupling, C*H*=) 4.43 (2H, s, PhC*H*$_2$OCH$_2$), 4.35 (2H, s, PhC*H*$_2$OCH$_2$) 4.21 (2H, d, *J* 6.4 Hz with finer coupling, PhCH$_2$OC*H*$_2$CH=), 4.12 (2H, d, *J* 1.3 Hz, PhCH$_2$OC*H*$_2$C=CH), 4.08 (2H, d, *J* 6.4 Hz, SiOC*H*$_2$CH=) 3.96 (2H, s, SiOC*H*$_2$C=CH), 0.82 (9H, s, ^{t}Bu), 0.81 (9H, s, ^{t}Bu), -0.03 (12H, 2s, 2x Me_2Si); δ_C(100 MHz, $CDCl_3$) 141.5, 136.8, 130.8, 128.4, 128.3, 127.7, 127.6, 126.3, 72.4, 72.1, 67.2, 66.0, 65.7, 60.6, 26.0, 25.9, -5.0, -5.3; m/z (CI, iso-butane) 582 (M^+), 475, 451, 417, 391, 367, 327, 237, 211, 181, 133, 107, 91; found: C, 70.2; H, 9.4. $C_{34}H_{54}O_4Si_2$ requires C, 70.1; H, 9.3%.

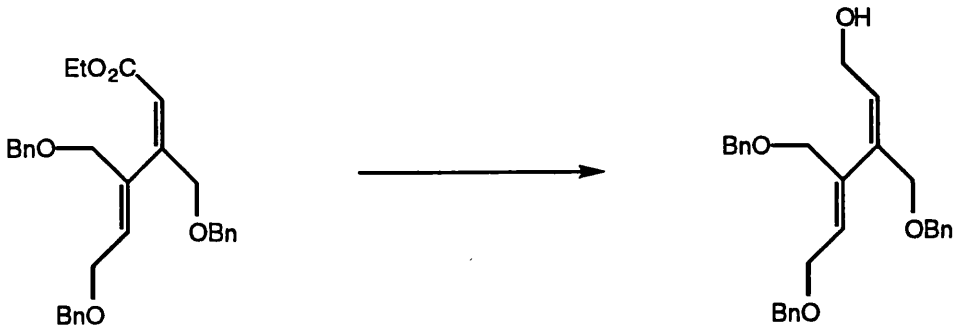
Preparation of (*Z*,*E*)-Ethyl 6-benzyloxy-(3,4-*bis*-(benzyloxymethyl))-2,4-hexadienoate 182



Vinyl iodide **157** (16.50 g, 47.69 mmol) was dissolved in dry DMF (170 ml). The solution was degassed by ultrasonication under argon flow before the addition of $ZnCl_2$ (13.00 g, 95.37 mmol), P(2-furyl)$_3$ (332 mg, 1.91 mmol) and $Pd_2(dba)_3$ (665 mg, 0.95 mmol). The solution was stirred under argon for 25 mins before the addition of the vinyl stannane **136** (31.93 g, 57.22 mmol) neat *via* cannula, rinsing in with DMF (10 ml). The mixture was heated at 65°C for 20h and then allowed to cool to RT. The mixture was then poured into a

separating funnel containing saturated aqueous NH_4Cl (150 ml) and Et_2O (200 ml). The ethereal layer was separated and the aqueous layer extracted with Et_2O (4 x 150 ml). The organics were combined and washed with saturated aqueous sodium thiosulfate (2 x 100 ml), H_2O (1 x 100 ml) and saturated brine (3 x 100 ml), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by FCC (15% EtOAc/petrol) to give the title compound **182** (19.93 g, 86%) as a pale yellow oil, ν_{max}(film) 3063, 3030, 2978, 2858, 1716, 1636, 1496, 1454, 1377, 1362, 1332, 1212, 1162, 1096, 1074, 1028, 872, 737 and 698 cm^{-1}; δ_H(270 MHz, $CDCl_3$) 7.25-7.17 (15H, m, Ph), 6.00 (1H, d, *J* 1.8 Hz, EtO_2CCH=), 5.56(1H, t, *J* 6.4 Hz, $BnOCH_2CH$=) 4.48 (2H, s, $PhCH_2OCH_2$), 4.43 (2H, s, $PhCH_2OCH_2$) 4.37 (2H, s, $PhCH_2OCH_2$), 4.15 (2H, s, CH_2O), 4.10-3.99 (6H, m, *includes* 4.08 (2H, d, *J* 6.4 Hz, $BnOCH_2CH$=), 4.04 (2H, q, *J* 7.0 Hz, $CO_2CH_2CH_3$)), 1.16 (3H, t, *J* 7.0 Hz, $CO_2CH_2CH_3$); δ_C(100 MHz, $CDCl_3$) 165.8 (s), 156.6 (s), 138.1 (s), 137.8 (s), 128.9 (d), 128.4 (d), 128.3 (d), 127.9 (d), 127.7 (d), 127.64 (d), 127.59 (d), 115.4 (d), 73.2 (t), 72.6 (t), 72.2 (t), 68.0 (t), 65.9 (t), 59.9 (t), 14.2 (q); m/z (CI, iso-butane) 487 (M^+), 441, 421, 395, 379, 365, 289, 273, 181, 107, 91; found: C, 76.4; H, 7.2. $C_{31}H_{34}O_5$ requires C, 76.5; H, 7.0%.

Preparation of (*Z*,*E*)-6-Benzyloxy-(3,4-*bis*-(benzyloxymethyl))-2,4-hexadienol 205

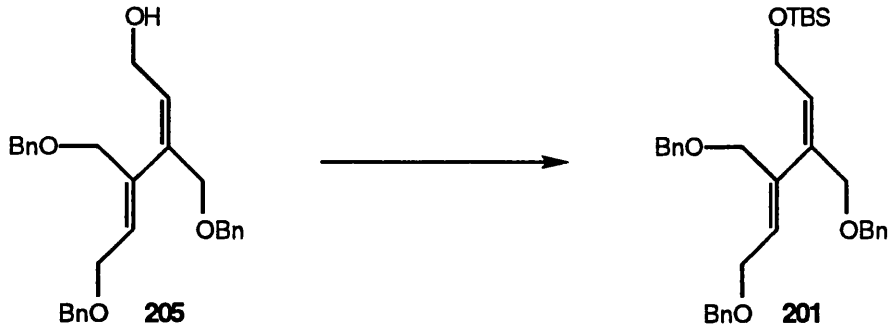


182 **205**

To a cooled (-40°C), stirred solution of dienic ester **182** (32.44 g, 66.75 mmol) in dry CH_2Cl_2 (150 ml) was added DIBAL-H (140 ml, 1.0 M solution in CH_2Cl_2, 140 mmol) dropwise under argon over 30 mins. The temperature was raised to -20°C and maintained for 1h, then quenched at -10°C by careful addition of dry MeOH (10 ml). The mixture was

then stirred at 0°C and then a solution of Rochelle's salt (33 ml of saturated solution in 200 ml H_2O) was cautiously added in 4 portions. The mixture was then allowed to warm to RT and stirred for 30 mins. The organic phase was separated and the aqueous phase was acidified with 2M HCl until all the aluminium salts had dissolved, then extracted with CH_2Cl_2 (4 x 150 ml). The organics were combined, then washed with 2M HCl (2 x 100 ml), H_2O (1 x 100 ml), saturated aqueous brine (2 x 100 ml), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual yellow oil was purified by FCC (50-70% Et_2O/petrol) to give the title compound **205** (27.86 g, 94%) as a clear oil, ν_{max}(film) 3421, 3062, 3029, 2856, 1496, 1453, 1362, 1093, 1071, 1027, 737 and 698 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.35-7.24 (15H, m, Ph), 5.90 (1H, t, *J* 7.1 Hz, C*H*=), 5.64 (1H, t, *J* 6.4 Hz, C*H*=), 4.48 (2H, s, PhCH_2O), 4.45 (2H, s, PhCH_2O), 4.43 (2H, s, PhCH_2O), 4.20-4.09 (4H, m, $PhCH_2OCH_2$ and =CHCH_2OH), 4.05 (4H, s, 2x $PhCH_2OCH_2$), 2.04 (1H, t, *J* 6.4 Hz, O*H*); δ_C(100 MHz, $CDCl_3$) 140.9, 138.1, 138.0, 137.5, 136.6, 130.7, 129.1, 128.5, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 73.0, 72.8, 72.2, 71.8, 66.1, 65.6, 59.1; m/z (+FAB) 467 (M+Na), 445 (M+H), 427, 391, 369, 351, 337, 321, 307, 289, 273, 259, 245, 229, 215; found: C, 78.7; H, 7.4. $C_{29}H_{32}O_4$ requires C, 78.4; H, 7.3%.

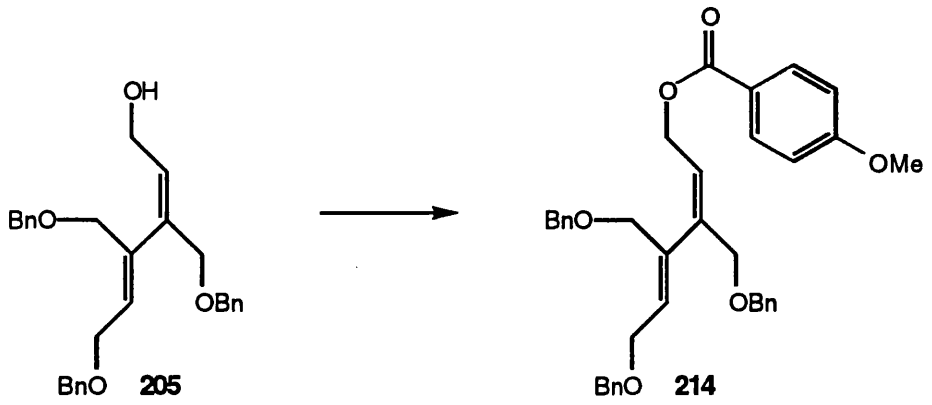
Preparation of (*Z*,*E*)-6-benzyloxy-(3,4-*bis*-(benzyloxymethyl))-1-(*tert*-butyldimethylsilyloxy)-2,4-hexadiene 201



To a stirred solution of dienic alcohol **205** (0.88 g, 1.98 mmol) in dry DMF (1.5 ml) under argon was added imidazole (336 mg, 4.94 mmol) followed by TBDMSCl (357 mg, 2.371 mmol). The mixture was stirred for 16.5h before quenching with saturated aqueous NH_4Cl. The mixture was then extracted with Et_2O (x3). The ethereal layers were combined then

washed with water (x3) and saturated aqueous brine (x3), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual yellow liquid was purified by FCC (15% Et_2O/petrol) to give the title compound **201** (0.96 g, 87%) as a clear liquid, ν_{max}(film) 3065, 3030, 2955, 2929, 2885, 2857, 1496, 1471, 1388, 1361, 1254, 1071, 1004, 939, 836, 780, 735, 697 and 670 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.30-7.20 (15H, m, Ph), 5.72 (1H, t, *J* 6.2 Hz, C*H*=), 5.62 (1H, t, *J* 6.4 Hz, C*H*=), 4.46 (2H, s, PhCH_2O),4.42 (2H, s, PhCH_2O), 4.36 (2H, s, PhCH_2O), 4.31 (2H, d, *J* 6.2 Hz, $PhCH_2OCH_2$), 4.13 (2H, d, *J* 6.2 Hz, $PhCH_2OCH_2$), 4.06 (2H, s, $PhCH_2OCH_2$), 4.05 (2H, s, $PhCH_2OCH_2$); δ_C(100 MHz, $CDCl_3$) 138.8, 138.3, 138.2, 138.1, 136.9, 131.0, 130.9, 128.4, 128.3, 128.1, 128.0, 127.8, 127.7, 127.6, 127.5, 73.0, 72.3, 72.0, 71.6, 66.4, 65.8, 60.5, 25.9, 18.3; m/z (+FAB) 531, 513, 489, 475, 461, 441, 423, 409, 379, 363, 351, 327, 283, 268, 253, 231, 221, 211, 195, 181, 147, 133, 113, 105, 91; found: C, 74.8; H, 8.4. $C_{35}H_{46}O_4Si$ requires C, 75.2; H, 8.3%.

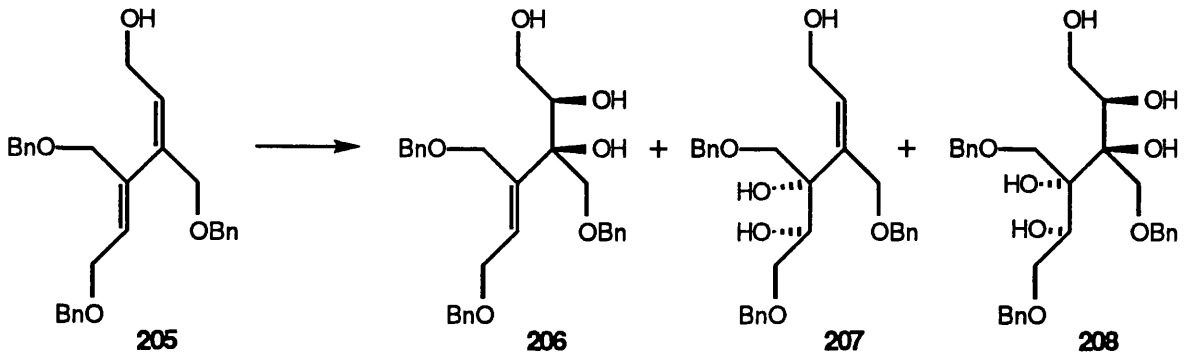
Preparation of (*Z*,*E*)-6-benzyloxy-(3,4-*bis*-(benzyloxymethyl))-1-(4-methoxy-benzoyloxy)-2,4-hexadiene 214



To a stirred solution of dienic alcohol **205** (255 mg, 0.57 mmol) in CH_2Cl_2 (1.0 ml) was added *p*-anisoyl chloride (118 mg, 0.69 mmol) followed by DMAP (cat) and Et_3N (120 µl, 0.86 mmol). After 3h, the mixture was partitioned between saturated aqueous NH_4Cl and CH_2Cl_2, and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 ml) and the combined organics were washed with 2M HCl (1 x 10 ml), H_2O (1 x 10 ml) and saturated aqueous brine (3 x 10 ml), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual yellow oil was purified by FCC (30% Et_2O/petrol) to give

the title compound **215** (0.96 g, 87%) as a clear liquid, ν_{max}(film) 3062, 3030, 2922, 2854, 1711, 1606, 1581, 1511, 1496, 1454, 1360, 1316, 1257, 1168, 1100, 1073, 1028, 848, 771, 738 and 698 cm^{-1}; δ_H (270 MHz, $CDCl_3$) ; m/z (+FAB) 601 (M+Na), 579 (M+H), 229, 181, 165, 135, 123, 107; observed: M+H, 579.2769. $C_{37}H_{39}O_6$ requires M+H, 579.2747.

Preparation of (2*R*, 3*R*, 4*E*)-2,3-dihydroxy-6-benzyloxy-(3,4-*bis*-(benzyloxymethyl))-4-hexen-1-ol 206 and (4*S*, 5*S*, 2*Z*)-4,5-dihydroxy-6-benzyloxy-(3,4-*bis*-(benzyloxymethyl))-2-hexen-1-ol 207 and (2*R*, 3*S*, 4*R*, 5*S*)-2, 3, 4, 5-tetrahydroxy-6-benzyloxy-(3,4-*bis*-(benzyloxymethyl))-hexan-1-ol 208 in the 2-phase system



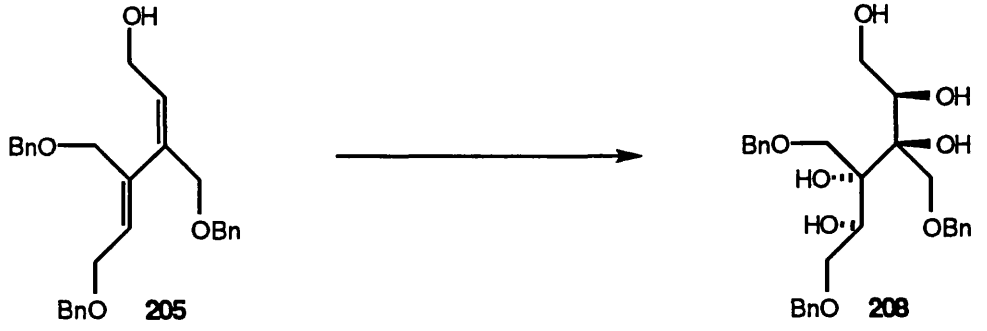
To a vigorously stirred, cooled (0°C) solution of dienic alcohol **205** (600 mg, 1.35 mmol) in ^tBuOH (2.2 ml) and H_2O (2.2 ml) was added AD-mix-β (1.89 g) followed by $K_2S_2O_8$ (729 mg, 2.7 mmol), $(DHQD)_2$-PHAL (105 mg, 0.13 mmol), OsO_4 (14 mg, 0.05 mmol) and $CH_3SO_2NH_2$ (256 mg, 2.70 mmol). The reaction was then allowed to warm to RT, and after 4d additional $(DHQD)_2$-PHAL (210 mg, 0.27 mmol) was added. After a further 5d, solid Na_2SO_3 (1.5 g) and EtOAc were added and the mixture stirred for 3h, then filtered and the solid residues re-extracted with EtOAc (x4). The filtrate and EtOAc extracts were combined and dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by FCC (80-100% Et_2O/petrol then 100% EtOAc) to give a mixture of the two triols **206** and **207** (504 mg) and the pentaol **208** as an 8:1 diastereomeric mixture (71 mg, 10%) all as clear oils; full data of pentaol as given in new AD procedure below; δ_H(270 MHz, $CDCl_3$) 7.38-7.21 (15H, m, Ph), 4.57-3.40 (18H, m), 2.67 (1H, bs, O*H*), 1.27-1.07 (2H, m); δ_C(100 MHz, $CDCl_3$) 137.6, 136.9, 136.2, 128.9, 128.8, 128.7, 128.6, 128.5,

128.4, 128.3, 128.2, 128.13, 128.05, 128.0, 127.9, 78.7, 77.7, 74.1, 73.9, 73.5, 73.2, 71.5, 71.4, 70.5, 70.4, 63.2, .

Typical one-phase AD:

To a stirred solution of dienic alcohol **205** (440 mg, 1.00 mmol) in acetone (2.0 ml) was added NMO (585 ml, 5.12 M solution in H_2O, 3.00 mmol) followed by $(DHQD)_2PHAL$ (39 mg, 0.05 mmol) and OsO_4 (2.5 mg, 0.01 mmol). After a total of 6d, solid sodium metabisulfite and CH_2Cl_2 was added and the mixture stirred for 1h, then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual brown oil was purified by FCC (75-100% EtOAc/petrol) to give the pentaol **208** (380 mg, 74%) as a clear oil, data as given in new AD procedure below.[147]

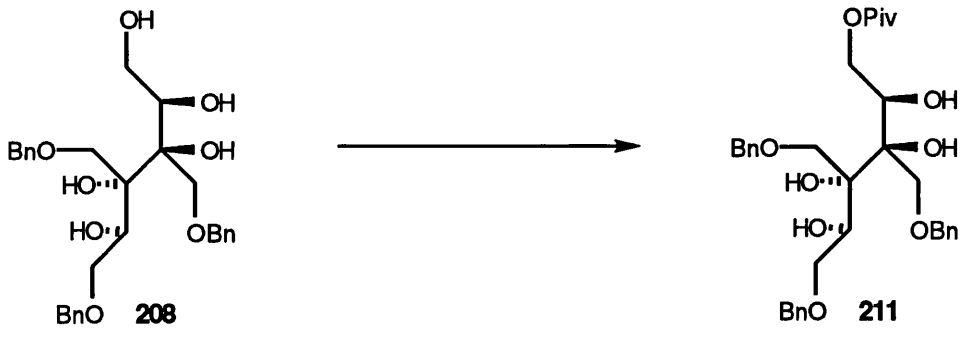
New AD procedure: Preparation of (2*R*, 3*R*, 4*R*, 5*S*)-2, 3, 4, 5-tetrahydroxy-6-benzyloxy-(3,4-*bis*-(benzyloxymethyl))-hexan-1-ol 208



A 1L 3-necked flask was charged with ^tBuOH (130 ml) and H_2O (160 ml). To this was added AD-mix-β (44 g) followed by $(DHQD)_2PHAL$ (1.23 g, 1.58 mmol), OsO_4 (80 mg, 0.32 mmol), $K_2S_2O_8$ (17.05 g, 63.06 mmol), and $CH_3SO_2NH_2$ (5.99 g, 63.06 mmol). This mixture was stirred well for 20 min, then cooled to 0°C before dropwise addition of dienic alcohol **205** (14.00 g, 31.53 mmol) in ^tBuOH (30 ml). The reaction came to RT after a few hours and stirring was continued for an additional 4 d at RT, after which time solid Na_2SO_3 (45 g) and EtOAc (300 ml) were added and the mixture stirred for 1h. The organic layer was separated and the aqueous layer extracted with EtOAc (3 x 150 ml). The combined organics

were washed sequentially with 2M KOH (3 x 100 ml), H_2O (2 x 100 ml) and brine (3 x 100 ml), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by FCC (80% Et_2O/petrol) to give the triols **206** and **207** (11.75 g, 78%). To a stirred solution of the triols **206** and **207** (11.75 g, 24.58 mmol) in acetone (47 ml) and H_2O (9 ml) was added $(DHQD)_2PHAL$ (957 mg, 1.23 mmol) and OsO_4 (63 mg, 0.25 mmol) followed by NMO (5.76 g, 49.16 mmol). After 3.5d solid $Na_2S_2O_5$ was added, followed by CH_2Cl_2 (100 ml). After a further 1h, the mixture was filtered, evaporated under reduced pressure, and azeotroped with benzene. The residual black oil was purified by FCC (75-100% EtOAc/petrol) to give the title compound **208** as a >9:1 diastereomeric mixture (7.30 g, 58%) as a clear oil, $[\alpha]_D^{19}$ +4.5 (*c* 1.0 in $CHCl_3$) @ *ca.* 76% ee; ν_{max}(film) 3423, 3013, 2928, 2872, 1494, 1453, 1366, 1214, 1078 and 754 cm^{-1}; δ_H(270 MHz, $CDCl_3$) 7.38-7.21 (15 H, m, Ph), 4.57-3.40 (18 H, m), 2.67 (1 H, bs, O*H*), 1.27-1.07 (2 H, m); δ_C(100 MHz, $CDCl_3$) 137.6, 136.9, 136.2, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.13, 128.05, 128.0, 127.9, 78.7, 77.7, 74.1, 73.9, 73.5, 73.2, 71.5, 71.4, 70.5, 70.4, 63.2; m/z (CI, iso-butane) 513 (M+H), 391, 369, 309, 279, 257, 229, 181, 154, 123, 107, 91, 69; found: C, 67.6; H, 7.1. $C_{29}H_{36}O_8$ requires C, 68.0; H, 7.1%.

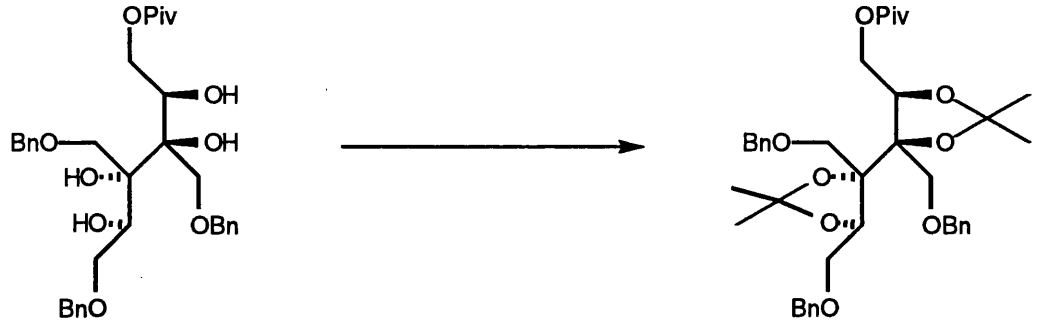
Preparation of (2*R*, 3*R*, 4*R*, 5*S*)-6-benzyloxy-(3,4-*bis*-(benzyloxymethyl))-1-pivaloyloxymethyl-hexan-2, 3, 4, 5-tetraol 211



To a cooled (0°C) stirred solution of pentaol **208** (14.58g, 28.48 mmol) in CH_2Cl_2 (100 ml) was added pivaloyl chloride (4.14 ml, 34.17 mmol) followed by DMAP (173 mg, 1.42 mmol) and pyridine (3.46 ml, 42.7 mmol). The reaction was then allowed to come to RT and stirred for 16h, then quenched by addition of saturated aqueous NH_4Cl (50 ml). The

organic layer was separated and the aqueous extracted with CH_2Cl_2 (4 x 50 ml). The organics were combined then washed with 2M HCl (3 x 50 ml), H_2O (2 x 50 ml), saturated aqueous $NaHCO_3$ (2 x 50 ml), H_2O (1 x 50 ml), saturated aqueous brine (2 x 50 ml), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by FCC (60% Et_2O/petrol) to give the title compound **211** (13.07 g, 77%) as a pale yellow oil, $[\alpha]_D^{19}$ +7.4 (*c* 1.0 in $CHCl_3$), ν_{max}(film) 3442, 3030, 2929, 2870, 1724, 1454, 1366, 1285, 1164, 1098, 911, 740 and 698 cm^{-1}; δ_H(400 MHz, $CDCl_3$) 7.37-7.17 (15H, m, *Ph*), 4.53-4.18 (10H, m, includes 4.52 (1H, d, *J* 11.2 Hz), 4.50(4H, s, OCH_2Ph), 4.40 (2H, dd, *J* 19.3 Hz and 6.5 Hz), 4.35 (1H, d, *J* 8.8 Hz), 4.32 (1H, d, *J* 11.7 Hz), 4.24 (1H, d, *J* 11.2 Hz)), 4.17 (1H, s, 3° O*H*), 4.07 (1H, s, 3° O*H*), 3.78 (2H, dd, *J* 16.6 Hz and 10.3 Hz), 3.66-3.63 (3H, m, includes 3.64 (1H, d, *J* 8.8 Hz)), 3.54 (1H, bs, 2° O*H*), 3.45 (1H, d, *J* 10.3 Hz), 1.20 (9H, s, ^tBu); δ_C(100 MHz, $CDCl_3$) 178.9 (s), 137.6 (s), 136.9 (s), 136.3 (s), 128.6 (d), 128.5 (d), 128.5 (d), 128.3 (d), 128.2 (d), 128.0 (d), 127.9 (d), 127.7 (d), 78.2 (s), 77.1 (s), 74.0 (t), 73.8 (t), 73.5 (t), 72.7 (d), 71.6 (d), 71.2 (t), 70.7 (t), 70.4 (t), 66.2 (t), 38.7 (s), 27.2 (q), 27.2 (q), 27.2 (q); found: C, 68.5; H, 7.6. $C_{34}H_{44}O_9$ requires C, 68.4; H, 7.4%.

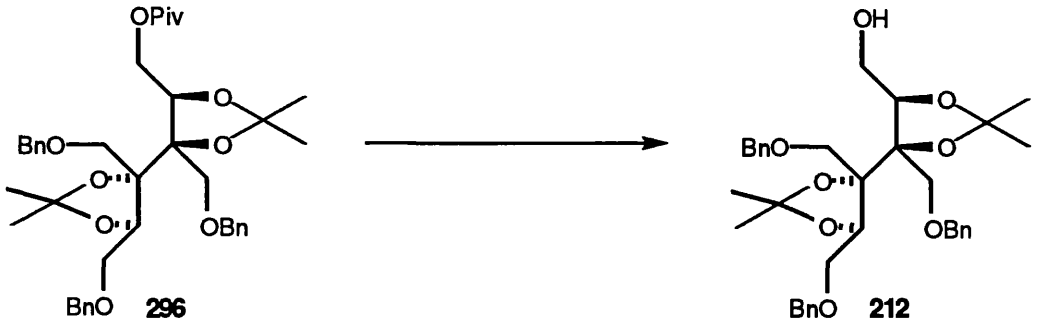
Preparation of (2*R*, 3*R*, 4*S*, 5*S*)-2,3,4,5-*bis*-(di-*O*-isopropylidene)-6-benzyloxy-(3,4-*bis*-(benzyloxymethyl))-1-(pivaloyloxymethyl)hexane 296



To a stirred solution of tetraol **211** (13.00 g, 21.81 mmol) in DMF (125 ml) containing *p*-TsOH (400 mg, catalytic amount) was added dropwise 2-methoxypropene (7.84 ml, 87.25 mmol). After 13h the reaction was quenched by addition of saturated aqueous $NaHCO_3$ (100 ml), then extracted with Et_2O (4 x 100 ml). The organics were combined and washed with

saturated aqueous $NaHCO_3$ (1 x 100 ml), H_2O (1 x 100 ml), saturated aqueous brine (2 x 100 ml), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by FCC (30% Et_2O/petrol) to give the title compound **296** (13.07 g, 77%) as a pale orange oil, $[\alpha]_D^{18}$ -5.1 (*c* 1.0 in $CHCl_3$), ν_{max}(film) 3029, 2977, 2930, 2860, 1730, 1455, 1372, 1248, 1211, 1155, 1086, 732 and 696 cm^{-1}; δ_H(270 MHz, $CDCl_3$) 7.40-7.20 (15H, m, Ph), 4.72-4.34 (10H, m, includes $PhCH_2OCH_2$ and $PivOCH_2$), 3.86-3.68 (4H, m, $PhCH_2OCH_2$), 3.62 (1H, d, *J* 10.8 Hz, $PhCH_2OCH_2$), 3.54 (1H, d, *J* 10.8 Hz, $PhCH_2OCH_2$), 1.42 (3H, s, CH_3), 1.35 (6H, s, 2 x CH_3), 1.32 (3H, s, CH_3), 1.21 (9H, s, ^tBu); *m/z* (+FAB) 677 (M+H), 662, 619 (M-tBu), 569, 555, 527, 497, 469, 453, 377, 363, 319, 255, 243, 211; found: C, 71.0; H, 7.8.$C_{40}H_{52}O_9$ requires C, 71.0; H, 7.7%.

Preparation of (2*R*, 3*R*, 4*S*, 5*S*)-2,3,4,5-*bis*-(di-*O*-isopropylidene)-6-benzyloxy-(3,4-*bis*-(benzyloxymethyl))-hexan-1-ol 212



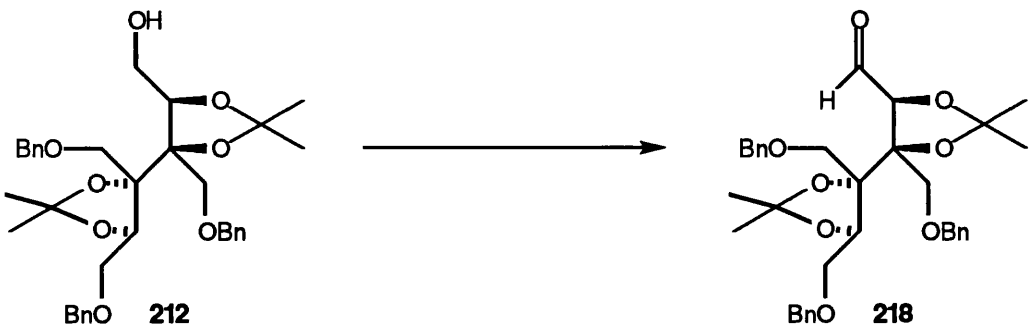
To a cooled (-78°C), stirred solution of pivaloate ester **296** (10.68 g, 15.79 mmol) in dry CH_2Cl_2 (85 ml) was added DIBAL-H (39.5 ml, 1.0 M solution in CH_2Cl_2, 39.5 mmol) dropwise under argon over 20 mins. After 45 mins the reaction was quenched by careful addition of dry MeOH (5 ml). The mixture was allowed to warm to 0°C and stirred at this temperature for 10 mins before careful addition of a solution of Rochelle's salt (33 ml of a saturated solution in 200 ml H_2O) in 3 portions. The mixture was then allowed to warm to RT and stirred for 30 mins. The organic phase was separated and the aqueous phase was acidified with 2M HCl until all the aluminium salts had dissolved, then extracted with CH_2Cl_2 (4 x 100 ml). The organics were combined, then washed with 2M HCl (1 x 100 ml), H_2O (1 x 100 ml), brine (2 x 100 ml), then dried ($MgSO_4$), filtered and evaporated under

reduced pressure. The residual yellow oil was purified by FCC (50% Et_2O/petrol) to give the title compound **212** (8.51 g, 91%) as a clear oil, $[\alpha]_D^{18}$ –9.1° (*c* 1.0 in $CHCl_3$) @ *ca.* 76% ee; ν_{max} (film) 3491, 3063, 3029, 2984, 2937, 2865, 1496, 1454, 1379, 1248, 1212, 1170, 1078, 1028, 1000, 911, 848, 737 and 698 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.37-7.20 (15H, m, *Ph*), 4.68 (1H, dd, *J* 8.0 Hz and 2.6 Hz), 4.61 (1H, d, *J* 12.3 Hz), 4.58-4.47 (5H, m, includes 4.50 (1H, d, *J* 12.6 Hz)), 4.39 (1H, d, *J* 11.9 Hz), 4.03-3.96 (1H, m), 3.92-3.84 (1H, m), 3.83-3.72 (5H, m, includes 3.81 (1H, d, *J* 19.6 Hz) and 3.75 (1H, d, *J* 19.6 Hz)), 3.50 (1H, d, *J* 11.0 Hz), 2.55 (1H, dd, *J* 7.7 Hz and 6.0 Hz, O*H*), 1.46 (3H, s, CH_3), 1.37 (3H, s, CH_3), 1.35 (3H, s, CH_3), 1.34 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 138.2 (s), 137.8 (s), 137.6 (s), 128.4 (d), 128.3 (d), 128.3 (d), 127.8 (d), 127.6 (d), 127.5 (d), 110.5 (s), 108.7 (s), 86.2 (s), 85.0 (s), 81.0 (d), 79.9 (d), 73.9 (t), 73.6 (t), 73.2 (t), 71.6 (t), 70.6 (t), 69.4 (t), 60.7 (t), 27.9 (q), 27.1 (q), 26.1 (q), 25.9 (q); m/z (FAB) 615 (M+Na), 593 (M+H), 573, 535, 413, 341, 251, 171, 149, 123; observed: M+Na, 615.2936. $C_{35}H_{44}NaO_8$ requires M+Na, 615.2934.

Preparation of Moshers ester 210

To a stirred solution of alcohol **212** (11 mg, 0.02 mmol) in CH_2Cl_2 (0.3 ml) was added DCC (6 mg, 0.03 mmol) followed by DMAP (catalytic) and (R)-(+)-α-methoxy-α-(trifluoromethyl)phenyl acetic acid (6 mg, 0.03 mmol). After 19h the mixture was diluted with CH_2Cl_2 (10 ml) and washed with 2M HCl (x2), H_2O (x1), saturated aqueous $NaHCO_3$ (x3), H_2O (x1), saturated aqueous brine (x2), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual oil was purified by FCC (30% Et2O/petrol) to give the Moshers ester derivative **210** (16 mg, 100%) as a clear oil. The enantiomeric excesses were determined by ^{19}F NMR analysis; the fluorine peaks are observed at -72.3 (major) and -72.2 ppm.

Preparation of (2*R*, 3*R*, 4*S*, 5*S*)-2,3,4,5-*bis*-(di-*O*-isopropylidene)-6-benzyloxy-(3,4-*bis*-(benzyloxymethyl))-hexan-1-al 218



Method A (Swern)

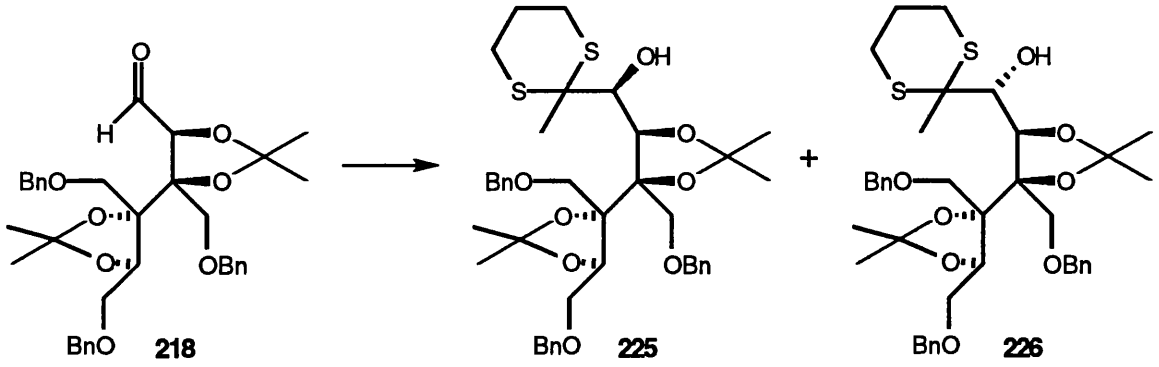
To a cooled (-78°C), stirred solution of oxalyl chloride (67µl, 0.76 mmol in dry CH_2Cl_2 (1.7 ml) was added a solution of anhydrous DMSO (107 µl, 1.52 mmol) in CH_2Cl_2 (1.5 ml) dropwise *via* cannula over 4 mins. After 14 mins a solution of alcohol **212** (300 mg, 0.51 mmol) in CH_2Cl_2 (1.4 ml) was added dropwise over 5 mins and stirred at -78°C for 25 mins. Then Et_3N (354 µl, 2.53 mmol) was added over 4 mins. After 1h, the reaction was quenched at -78°C by addition of saturated aqueous NH_4Cl (0.8 ml) and the mixture was then allowed to warm to RT. The organics were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 5 ml). The organics were combined and washed with saturated aqueous NH_4Cl (2 x 5 ml), H_2O (1 x 5 ml), saturated aqueous brine (1 x 5 ml), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual yellow oil was purified by FCC (30% Et_2O/petrol) to give the title compound **218** (248 mg, 83%) as a clear oil, $[\alpha]_D^{27}$ -15.1 (*c* 0.94 in $CHCl_3$) @68% ee, υ_{max}(film) 3087, 3062, 3029, 2982, 2934, 2858, 1729, 1496, 1454, 1380, 1247, 1215, 1172, 1096, 1028, 932, 910, 859, 737 and 698 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 9.70 (1H, s, C*H*O), 7.36-7.23 (15H, m, *Ph*), 4.61 (1H, d, *J* 12.3 Hz), 4.55 (1H, d, *J* 11.9 Hz), 4.51 (1H, d, *J* 11.9 Hz), 4.46-4.41 (3H, m), 4.31 (1H, d, *J* 12.1 Hz), 3.90 (1H, d, *J* 10.5 Hz), 3.85 (1H, d, *J* 10.5 Hz), 3.71 (1H, dd, *J* 10.5 Hz and 1.8 Hz), 3.60 (1H, dd, *J* 10.5 Hz and 8.3 Hz), 3.52 (1H, d, *J* 9.9 Hz), 3.48 (1H, d, *J* 9.9 Hz), 1.41 (3H, s, C*H*$_3$), 1.39 (3H, s, C*H*$_3$), 1.37 (3H, s, C*H*$_3$), 1.35 (3H, s, C*H*$_3$); δ_C (125 MHz, $CDCl_3$) 195.5, 138.0, 137.5, 128.4, 128.3, 127.9, 127.8, 127.8, 127.7, 127.6, 110.1, 109.9, 86.9, 85.2, 83.5, 79.5, 73.8, 73.3, 73.1, 70.6, 69.4, 68.9, 28.6, 27.0, 26.4, 26.0; m/z (+FAB) 614, 592, 335, 277, 257,

243, 227, 213, 197, 191, 181, 165, 157, 149, 141, 131, 123, 109; found C, 71.3; H, 7.2. $C_{35}H_{42}O_8$ requires C, 71.2; H, 7.2%.

Method B (Dess -Martin Oxidation)

To a stirred solution of alcohol **212** (250 mg, 0.42 mmol) in CH_2Cl_2 (5 ml) was added a solution of Dess-Martin periodinane reagent (233 mg, 0.55 mmol) in anhydrous CH_2Cl_2 (7 ml) *via* cannula. After 10 mins "wet" CH_2Cl_2 (6.5 ml of a 1µl H_2O/1 ml CH_2Cl_2 solution) was added in portions over a 45 mins time period. The reaction was then concentrated *in vacuo* before the addition of a 1:1 solution of saturated aqueous $NaHCO_3$ / 1M $Na_2S_2O_3$ (25 ml) and Et_2O (25 ml). The mixture was stirred for 25 mins, then the organics were separated and the aqueous layer extracted with Et_2O (3 x 20 ml). The organics were combined and washed with H_2O (1 x 25 ml), saturated brine (3 x 25 ml), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual yellow oil was purified by FCC (20% Et_2O/petrol) to give the title compound **218** (225mg, 91%) as a clear oil, data as above.

Preparation of (1'*S*, 2'*R*, 3'*R*, 4'*S*, 5'*S*)-2-[(2', 3', 4', 5'-*bis*-(di-*O*-isopropylidene))-6'-benzyloxy-3',4'-*bis*-(benzyloxymethyl))-1'-hydroxy-hexyl]-2-methyl-1,3-dithiane 225 and (1'*R*, 2'*R*, 3'*R*, 4'*S*, 5'*S*)-2-[(2', 3', 4', 5'-*bis*-(di-*O*-isopropylidene))-6'-benzyloxy-3',4'-*bis*-(benzyloxymethyl))-1'-hydroxy-hexyl]-2-methyl-1,3-dithiane 226.



To a cooled (-50°C), stirred solution of 2-methyl-1,3-dithiane (87 µl, 0.79 mmol) in THF (1.5 ml, making 0.5 M solution) was added ^{n}BuLi (332 µl, 2.5 M solution in hexanes, 0.83 mmol) dropwise over 3 mins. Then mixture was then allowed to warm to -20°C and

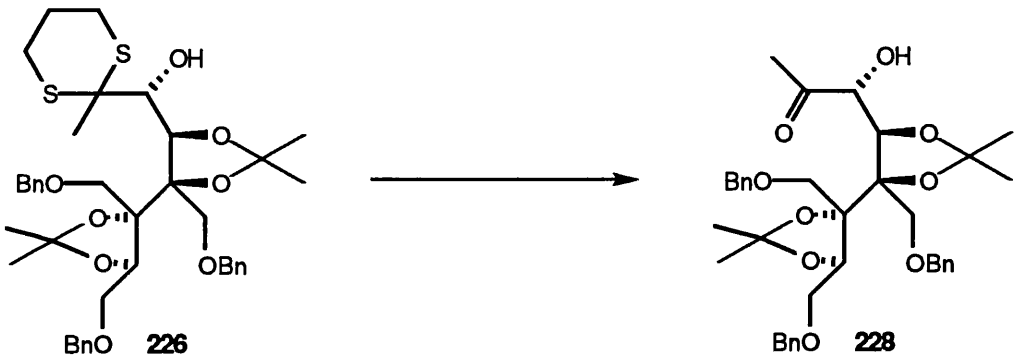
maintained at this temperature for 1.5h. The contents of the flask was then cooled to -78°C before the dropwise addition of aldehyde **218** (186 mg, 0.31 mmol) in THF (1.4 ml) *via* cannula over 2 mins. After 20 mins the reaction was quenched at -78°C by addition of H_2O (5 ml) and CH_2Cl_2 (10 ml), then allowed to warm to RT and poured into a separating funnel containing 2M KOH (2 ml). The organics were separated and the aqueous extracted with CH_2Cl_2 (5 x 5 ml). The organics were combined, washed with 2M KOH (1 x 10 ml), H_2O (1 x 10 ml), sat. brine (2 x 10 ml), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual yellow oil was purified by FCC (30% Et_2O/petrol) to give the title compound **225** (114 mg, 44%) and **226** both as clear glassy solids.

Less polar **225**, $[\alpha]_D^{28}$ -11.2 (*c* 2.1 in $CHCl_3$) @ *ca.* 76% ee; ν_{max}(film) 3432, 3026, 2979, 2925, 2861, 1453, 1370, 1247, 1214, 1171, 1076, 909, 852, 736 and 698 cm^{-1} ; δ_H (500 MHz, $CDCl_3$) 7.39-7.24 (15H, m, Ph), 4.95 (1H, d, *J* 9.0 Hz), 4.73 (1H, dd, *J* 7.4 Hz and 2.7 Hz), 4.66-4.61 (3H, m), 4.53 (1H, d, *J* 4.4 Hz), 4.50 (1H, d, *J* 4.0 Hz), 4.48 (1H, d, *J* 4.4 Hz), 4.45 (1H, s), 4.35 (1H, dd, *J* 8.9 Hz and 3.5 Hz), 4.24 (1H, d, *J* 3.5 Hz), 3.97 (1H, d, *J* 10.6 Hz), 3.84-3.78 (4H, m), 3.56 (1H, d, *J* 10.8 Hz), 3.35 (1H, ddd, *J* 13.6 Hz, 10.6 Hz and 3.1 Hz), 3.14 (1H, ddd, *J* 13.6 Hz, 10.5 and 3.0 Hz), 2.69 (1H, ddd, *J* 9.6 Hz, 6.2 Hz and 3.1 Hz), 3.14 (1H, ddd, *J* 13.6 Hz, 10.5 Hz and 3.0 Hz), 2.69 (1H, ddd, *J* 9.6 Hz, 6.2 Hz and 3.4 Hz), 2.58 (1H, ddd, *J* 9.4 Hz, 6.2 Hz and 3.1 Hz), 2.07-1.96 (1H, m), 1.93-1.82 (1H, m), 1.50 (3H, s), 1.49 (3H, s), 1.37 (3H, s), 1.36 (3H, s), 1.24 (3H, s); δ_C (125 MHz, $CDCl_3$) 138.2 (s), 138.0 (s), 137.5 (s), 128.4 (d), 128.2 (d), 128.0 (d), 127.8 (d), 127.8 (d), 127.7 (d0, 127.6 (d), 127.5 (d), 127.5 (d0, 110.9 (s), 108.3 (s), 86.0 (s), 85.4 (s), 80.6 (d), 79.8 (d), 78.9 (d), 74.0 (t), 73.5 (t), 73.2 (t), 70.7 (t), 70.2 (t), 69.0 (t), 52.5 (s), 28.4 (t), 27.7 (q), 27.0 (q), 27.0 (t), 26.1 (q), 25.7 (q), 25.6 (q), 24.8 (t); m/z (+FAB) 747 (M+Na), 725 (M+H), 667, 591, 469, 335, 271, 243, 227, 213, 197, 181, 165, 149, 123; found: C, 66.6; H, 7.5. $C_{40}H_{52}O_8S_2$ requires C, 66.3; H, 7.2%.

More polar **226**, $[\alpha]_D^{27}$ -8.3 (*c* 0.85 in $CHCl_3$), υ_{max}(film) 3468, 3029, 2983, 2925, 2853, 1496, 1454, 1377, 1247, 1211, 1171, 1089, 910, 734 and 698 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.37-7.20 (15H, m, *Ph*), 4.91 (1H, s), 4.77 (1H, d, *J* 7.3 Hz), 4.66 (1H, d, *J* 12.5 Hz), 4.57 (1H, d, *J*11.9 Hz), 4.54 (2H, s), 4.53 (1H, d, *J* 12.5 Hz), 4.43 (2H, d, *J* 11.9 Hz), 4.16 (1H, d, *J* 10.9 Hz), 3.91 (1H, d, *J* 10.2 Hz), 3.87 (1H, d, *J* 7.3 Hz), 3.78 (2H, d, *J* 10.2

Hz), 3.60 (1H, d, *J* 10.9 Hz), 3.03 (1H, bs), 2.84-2.71 (2H, m), 2.57-2.54 (1H, m), 2.32-2.30 (1H, m), 1.90-1.70 (2H, m), 1.48 (3H, s), 1.42 (3H, s), 1.38 (3H, s), 1.37 (3H, s), 1.35 (3H, s); δ_C (125 MHz, $CDCl_3$) 138.7, 138.1, 137.9, 128.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 127.7, 127.5, 127.4, 110.2, 108.8, 86.3, 81.1, 75.9, 73.9, 73.6, 73.0, 71.4, 69.2, 66.1, 54.1, 28.3, 27.3, 26.2, 26.1, 25.9, 24.3, 22.2; m/z (+FAB) 747 (M+Na), 725 (M+H), 667, 591, 559, 469, 341, 335, 271, 243, 227, 213, 197, 181, 165, 149, 123; observed: M+H, 725.3206. $C_{40}H_{53}O_8S_2$ requires M+H, 725.3182.

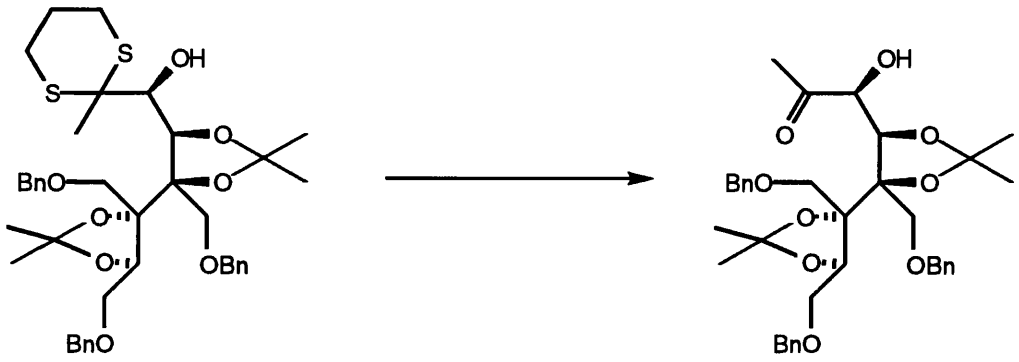
Preparation of (3*R*, 4*R*, 5*R*, 6*S*, 7*S*)-(4, 5, 6, 7-*bis*-(di-*O*-isopropylidene))-8-benzyloxy-5, 6-*bis*-(benzyloxymethyl))-3-hydroxy-octan-2-one 228



To a stirred solution of dithiane **226** (150 mg, 0.21 mmol) in THF (0.75 ml) was added H_2O (150 µl) followed by $CaCO_3$ (49 mg, 0.54 mmol), then a solution of $Hg(ClO_4)_2$ (115 µl, 4M solution in H_2O, 0.50 mmol) was added dropwise. After 30 mins saturated aqueous $NaHCO_3$ (2 ml) and Et_2O (5 ml) were added and the mixture stirred for 10 mins. The organics were then separated and the aqueous layer extracted with Et_2O (3 x 5 ml). The organics were combined and washed with H_2O (3 x 5 ml), saturated aqueous brine (3 x 5 ml), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual yellow oil was purified by FCC (30% Et_2O/petrol containing 1% Et_3N, then eluted with 30% Et_2O/petrol) to give the title compound **228** (120 mg, 92%) as a clear oil, $[\alpha]_D^{23}$ -3.7 (*c* 0.64 in $CHCl_3$) @ *ca.* 76% ee; ν_{max}(film) 3461, 3067, 3029, 3983, 2926, 2855, 1722, 1496, 1454, 1372, 1248, 1211, 1170, 1074, 1028, 1000, 896, 852, 737, 698 and 665 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.35-7.21 (15H, m, *Ph*), 4.71-4.66 (2H, m), 4.63 (1H, d, *J* 12.4 Hz), 4.56-4.46

(4H, m), 4.67 (1H, d, *J* 11.6 Hz), 4.32 (1H, dd, *J* 5.4 Hz and 2.1 Hz), 3.97 (1H, d, *J* 10.8 Hz), 3.94 (1H, d, *J* 10.1 Hz), 3.81-3.72 (2H, m), 3.68-3.61 (2H, m), 3.55 (1H, d, *J* 10.8 Hz), 2.18 (3H, s, $COCH_3$), 1.45 (3H, s, CH_3), 1.44 (3H, s, CH_3), 1.36 (3H, s, CH_3), 1.34 (3H, s, CH_3); δ_C (125 MHz, $CDCl_3$) 207.8 (s), 138.5 (s), 137.9 (s), 137.7 (s), 128.4 (d), 128.3 (d), 128.0 (d), 127.9 (d), 127.8 (d), 127.6 (d), 127.5 (d), 110.3 (s), 108.6 (s), 87.1 (s), 85.2 (s), 80.2 (d), 79.7 (d), 74.7 (d), 73.7 (t), 73.6 (t), 73.1 (t), 72.8 (t), 71.0 (t), 69.2 (t), 28.2 (q), 26.9 (q), 26.3 (q), 26.0 (q), 25.8 (q); m/z (+FAB) 657 (M+Na), 635 (M+H), 341, 293, 213, 197, 181, 149, 123; Found: C, 70.1; H, 7.3. $C_{37}H_{46}O_9$ requires C, 70.1; H, 7.2%.

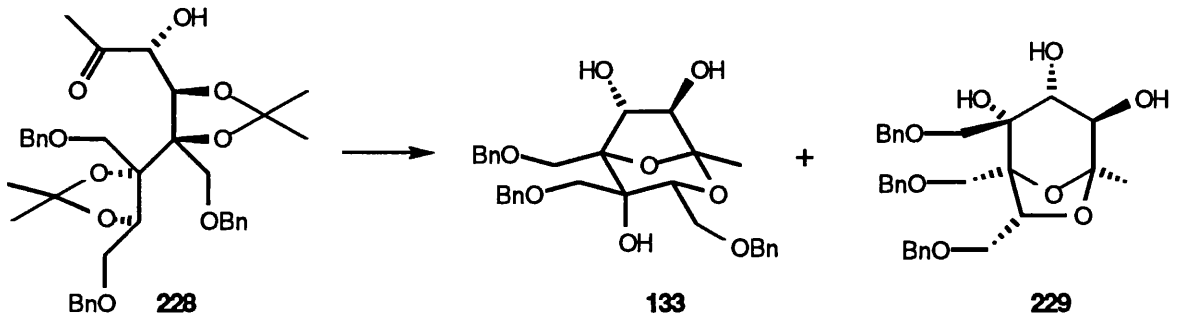
Preparation of (3*S*, 4*R*, 5*R*, 6*S*, 7*S*)-(4, 5, 6, 7-*bis*-(di-*O*-isopropylidene))-8-benzyloxy-5, 6-*bis*-(benzyloxymethyl))-3-hydroxy-octan-2-one 227



To a stirred solution of dithiane **225** (120 mg, 0.17 mmol) in THF (0.75 ml) was added H_2O (150 µl) followed by $CaCO_3$ (39 mg, 0.43 mmol), then a solution of $Hg(ClO_4)_2$ (92 µl, 4M solution in H_2O, 0.40 mmol) was added dropwise. After 30 mins saturated aqueous $NaHCO_3$ (2 ml) and Et_2O (5 ml) were added and the mixture stirred for 10 mins. The organics were then separated and the aqueous layer extracted with Et_2O (3 x 5 ml). The organics were combined and washed with H_2O (3 x 5 ml), saturated brine (3 x 5 ml), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual yellow oil was purified by FCC (30% Et_2O/petrol containing 1% Et_3N, then eluted with 30% Et_2O/petrol) to give the title compound **227** (90 mg, 84%) as a clear oil, $[\alpha]_D^{31}$ +4.3 (*c* 1.2 in $CHCl_3$) @ *ca.* 76% ee; ν_{max}(film) 3458, 3063, 3029, 2937, 2861, 1716, 1496, 1454, 1369, 1249, 1213, 1170, 1077, 1028, 998, 910, 852, 737 and 698 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.35-7.25 (15H,

m, *Ph*), 4.78-4.71 (2H, m), 4.65-4.50 (6H, m), 4.30 (1H, d, *J* 9.3 Hz), 3.87-3.72 (6H, m), 3.61 (1H, d, *J* 10.7 Hz), 2.07 (3H, s, C(O)CH_3), 1.49 (3H, s, CH_3), 1.38 (3H, s, CH_3), 1.37 (3H, s, CH_3), 1.33 (3H, s, CH_3); δ_C (125 MHz, $CDCl_3$) 208.1 (s), 138.1 (s), 137.7 (s), 137.6 (s), 128.4 (d), 128.3 (d), 127.9 (d), 127.8 (d), 127.7 (d), 127.6 (d), 110.5 (s), 109.0 (s), 86.3 (s), 86.2 (s), 79.8 (d), 79.2 (d), 73.9 (t), 73.6 (d+t), 73.3 (t), 70.9 (t), 70.2 (t), 69.1 (t), 28.1 (q), 27.4 (q), 27.0 (q), 26.1 (q), 25.8 (q); m/z 657 (M+Na), 181, 154, 133, 109, 91; found: C, 70.1; H, 7.5. $C_{37}H_{46}O_9$ requires C, 70.1; H, 7.2%.

Preparation of (1S, 3R, 4S, 5R, 6R, 7R)-4,6,7-trihydroxy-3,4,5-tri-(benzyloxymethyl)-1-methyl-2,8-dioxabicyclo[3.2.1]octane 133 and (1*S*, 2*R*, 3*R*, 4*R*, 5*S*, 6*R*)-2, 3, 4-trihydroxy-4, 5, 6-tri-(benzyloxymethyl)-1-methyl-7,8-dioxabicyclo[3.2.1]octane 229



Nicolaou conditions

Hydroxy ketone **228** (80 mg, 0.126 mmol) was treated with 2% HCl/MeOH (0.5 ml) and heated at 60°C for 18h. The mixture was then allowed to cool to RT and quenched by addition of saturated aqueous $NaHCO_3$ (2 ml) and diluted with CH_2Cl_2 (10 ml). The organics were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 5 ml). The organics were combined, then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual brown oil was purified by FCC (50-100% EtOAc/petrol) to give the title compound **133** (30 mg, 45%) as a white solid and **229** (32 mg, 47%) as a clear oil.

Less polar **133**, $[\alpha]_D^{24}$ -1.5 (*c* 0.3 in $CHCl_3$) @ *ca.* 76% ee; ν_{max}(film) 3444, 3020, 2918, 2868, 1445, 1386, 1353, 1205, 1170, 1093, 1023, 900, 730, 696 and 666 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.36-7.24 (13H, m, Ph), 7.17-7.15 (2H, m, Ph), 4.79 (1H, t *J* 2.9 Hz, H6), 4.53 (2H, dd, *J* 18.6 Hz and 12.2 Hz, CH_2OCH_2OPh), 4.47 (2H, dd, *J* 16.4 Hz and

11.2 Hz, CH_2OCH_2OPh), 4.39 (1H, dd, *J* 5.4 Hz and 3.4 Hz, H3), 4.31 (2H, s, CH_2OCH_2OPh), 4.00 (1H, bs, H7), 3.92 (1H, d, *J* 9.8 Hz, one of CH_2OCH_2OPh @C4 or C5), 3.78 (1H, dd, *J* 11.2 Hz and 3.4 Hz, one of CH_2OCH_2OPh @C3), 3.64-3.57 (3H, m, one of CH_2OCH_2OPh @C3 and CH_2OCH_2OPh @C4 or C5), 3.52-3.43 (3H, m, includes 3.44 (1H, s, 4-O*H*), one of CH_2OCH_2OPh @C4 or C5 and 7-O*H*), 2.47 (1H, d, *J* 5.4 Hz, 6-O*H*), 1.50 (3H, s, CH_3); δ_C (100MHz, $CDCl_3$) 138.0 (s), 137.6 (s), 128.6 (d), 128.3 (d), 128.2 (d), 128.0 (d), 127.7 (d), 127.7 (d), 127.6 (d), 127.6 (d), 127.5 (d), 104.1 (s), 86.7 (s), 84.7 (d), 79.3 (t), 73.9 (t), 73.5 (t), 73.2 (t), 72.9 (d), 70.8 (s), 69.5 (t), 69.3 (t), 68.4 (t), 22.2 (q); m/z (+FAB) 559 (M+Na), 537 (M+H), 509, 413, 391, 259, 181, 149, 109; observed: M+Na, 559.2288. $C_{31}H_{36}NaO_8$ requires M+Na, 559.2308.

More polar **229**, $[\alpha]_D^{21}$ +44.0 (*c* 1.0 in $CHCl_3$) @ *ca.* 76% ee; ν_{max}(film) 3440, 3062, 3029, 2921, 2855, 1496, 1454, 1382, 1271, 1256, 1207, 1095, 1027, 904, 834, 738, 698 and 666 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.29-7.10 (15H, m, Ph), 4.58-4.44 (5H, m, includes 4.46 (1H, s, 5-OH), three of $PhCH_2O$ and H3), 4.34 (1H, d, *J* 12.2 Hz, one of $PhCH_2O$), 4.26 (1H, d, *J* 11.7 Hz, one of $PhCH_2O$), 4.21 (1H, d, *J* 11.7 Hz, one of $PhCH_2O$), 3.88 (1H, d, *J* 10.7 Hz, one of $PhCH_2OCH_2$), 3.70 (1H, d, *J* 10.7 Hz, one of $PhCH_2OCH_2$), 3.68 (1H, d, *J* 9.8 Hz, one of $PhCH_2OCH_2$), 3.63 (1H, t, *J* 9.8 Hz, becomes d, *J* 7.8 Hz on D_2O shake, H6 or H7), 3.53 (1H, t, *J* 8.3 Hz, becomes d, *J* 7.8 Hz on D_2O shake, H6 or H7), 3.42-3.24 (3H, m, $PhCH_2OCH_2$), 2.41 (1H, d, *J* 9.8 Hz, 6-O*H* or 7-O*H*), 2.01 (1H, d, *J* 8.3 Hz, 6-O*H* or 7-O*H*), 1.47 (3H, s, CH_3); m/z (+FAB) 559 (M+Na), 537 (M+H), 391, 181, 167, 149, 131, 123, 109; found: C, 69.7; H, 7.0. $C_{31}H_{36}O_8$ requires C, 69.4; H, 6.8%.

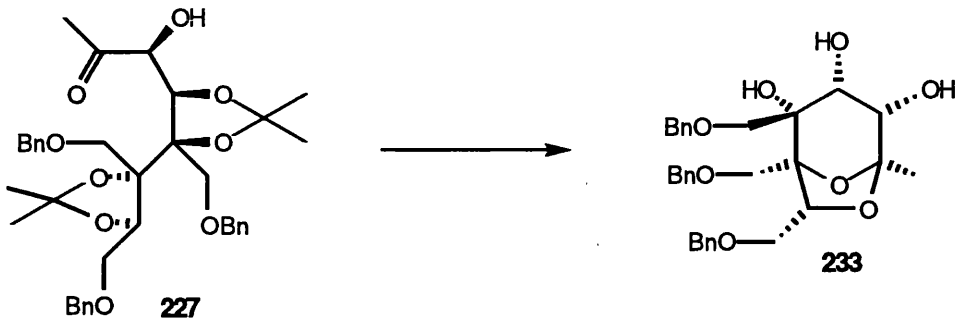
Evans conditions

Hydroxy ketone **228** (22 mg, 0.04 mmol) was stirred in CH_2Cl_2 (200 µl) : TFA (100 µl) : H_2O (10 µl) at RT for 16h. The mixture was then quenched by addition of saturated aqueous $NaHCO_3$ (2 ml) and diluted with CH_2Cl_2 (10 ml). The organics were separated and the aqueous layer extracted with CH_2Cl_2 (4 x 5 ml). The organics were combined, washed with saturated aqueous brine (1 x 10 ml), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual orange oil was purified by FCC (50-100% EtOAc/petrol) to

give the title compound **133** (7 mg, 38%) as a white solid and **229** (7 mg, 38%) as a clear oil. The data obtained were identical to those given above.

Preparation of (1*S*, 2*S*, 3*R*, 4*R*, 5*S*, 6*R*)-2, 3, 4-trihydroxy-4, 5, 6-tri-(benzyloxymethyl)-1-methyl-7,8-dioxabicyclo[3.2.1]octane 233

Nicolaou conditions



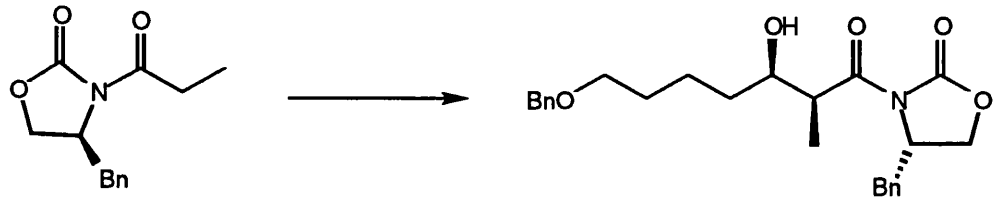
Hydroxy ketone **227** (34 mg, 0.05 mmol) was treated with 2% HCl/MeOH (0.4 ml) and stirred at RT for 13h, then heated at 50°C for 5h. The mixture was then allowed to cool to RT and quenched by addition of saturated aqueous $NaHCO_3$ (2 ml) followed by dilution with CH_2Cl_2 (10 ml). The organics were separated and the aqueous extracted with CH_2Cl_2 (3 x 5 ml). The organics were combined and washed with saturated brine (1 x 10 ml), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual brown oil was purified by FCC (50% EtOAc/petrol) to give the title compound **233** (20 mg, 70%) as a clear oil, $[\alpha]_D^{30}$ +29.2 (*c* 1.1 in $CHCl_3$) @ *ca.* 76% ee; ν_{max}(film) 3420, 3033, 2922, 2864, 1496, 1453, 1382, 1205, 1096, 1028, 870, 737, 698 and 667 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.39-7.20 (13H, m, Ph), 7.19-7.14 (2H, m, Ph), 4.80 (1H, d, *J* 1.5 Hz, 5-O*H*), 4.55-4.43 (4H, m, H3 and PhCH_2OCH_2), 4.41 (1H, d, *J* 11.7 Hz, PhCH_2OCH_2), 4.29 (1H, d, *J* 11.7 Hz, PhCH_2OCH_2), 4.23 (1H, d, *J* 11.7 Hz, PhCH_2OCH_2), 3.97 (2H, d, *J* 10.7 Hz, on D_2O shake becomes 3.97 (1H, d, *J* 10.3 Hz, PhCH_2OCH_2), 3.96 (1H, d, *J* 4.4 Hz , H6 or H7)), 3.82 (1H, d, *J* 9.8 Hz, PhCH_2OCH_2), 3.75 (1H, d, *J* 10.7 Hz, PhCH_2OCH_2), 3.57 (1H, dd, *J* 11.7 Hz and 4.4 Hz, on D_2O shake becomes 3.56 (1H, d, *J* 4.4 Hz, H6 or H7), 3.42-3.27 (4H, m, three of PhCH_2OCH_2 and 6-O*H* or 7-O*H*), 2.85 (1H, d, *J* 10.7 Hz, 6-O*H* or 7-O*H*), 1.56

(3H, s, CH_3); δ_C (100MHz, $CDCl_3$) 137.7 (s), 137.5 (s), 136.2 (s), 128.6 (d), 128.4 (d), 128.4 (d), 128.3 (d), 128.2 (d), 128.1 (d), 127.8 (d), 127.8 (d), 127.7 (d), 108.2 (s), 84.4 (s), 77.2 (s), 76.0 (d), 74.3 (t), 74.1 (d), 73.8 (t), 73.3 (t), 70.6 (t), 69.7 (t), 69.1 (t), 64.9 (d), 21.1 (q); m/z (+FAB) 559 (M+Na), 537 (M+H), 341, 327, 281, 267, 221, 207, 193, 181, 165, 147, 131, 123, 111; observed: M+H, 537.2496. $C_{31}H_{37}O_8$ requires M+H, 537.2488.

Evans conditions

Hydroxy ketone **228** (26 mg, 0.041 mmol) was stirred in CH_2Cl_2 (200 µl) : TFA (100 µl) : H_2O (10 µl) at RT for 23h, then concentrated *in vacuo*. The residual orange oil was purified by FCC (50% EtOAc/petrol) to give the title compound **234** (15 mg, 69%), data as above.

Preparation of (2'*S*, 3'*R*, 4*S*)-4-benzyl-3-(3'-hydroxy-2'-methyl-1'-oxaheptyl)-2-oxazolidinone 258

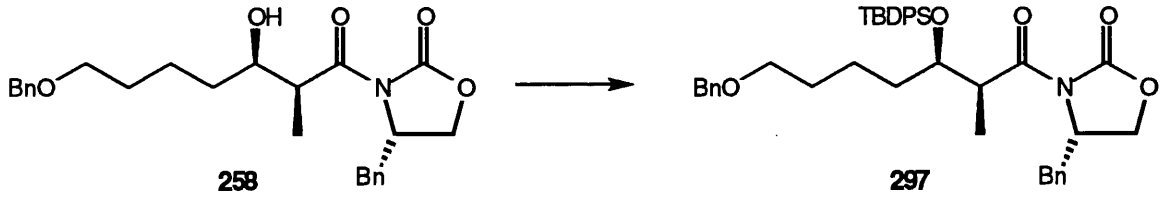


262 **258**

To a cooled (-78°C), stirred solution of (*S*)-3-(1-oxapropyl)-4-(phenylmethyl)-2-oxazolidinone **262** (20.00 g, 0.10 mol) in CH_2Cl_2 (360 ml) was added dibutylboron triflate (26.5 ml, 105 mmol) dropwise over 15 mins, followed by Et_3N (15.9 ml, 115 mmol) dropwise over 10 mins. The reaction was brought to 0°C and stirred at this temperature for 45 mins. After recooling the contents to -78°C, a pre-cooled (-78°C) solution of 5-(benzyloxy)-pentanal (18.21 g, 107 mmol) in CH_2Cl_2 (70 ml) was added dropwise *via* cannula over 50 mins. The reaction was allowed to come to RT overnight, and after a total reaction time of 13h, quenched at 0°C by addition of pH7 phosphate buffer (100 ml) and MeOH (270 ml). Then a 2:1 mixture of MeOH/ 30% H_2O_2 (270 ml) was cautiously added and the resultant milky white suspension was stirred at 0°C for 1/2h then at RT for 1h. The

mixture was then poured into a separating funnel containing H_2O (350 ml) and the organics separated. The aqueous layer was extracted with CH_2Cl_2 (4 x 200 ml). The organics were combined then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual pale orange oil was purified by FCC (50% EtOAc/petrol) to give the title compound **258** (34.43 g, 81%) as a clear oil. The data obtained were consistent with the literature;[32b] $[\alpha]_D^{21}$ +101.9 (*c* 0.41 in CH_2Cl_2); ν_{max}(film) 3512, 2938, 2861, 1779, 1695, 1496, 1454, 1385, 1210, 1109 and 738 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.35-7.33 (6H, m, *Ph*), 7.30-7.26 (2H, m, *Ph*), 7.20 (2H, d, *J* 7.2 Hz, *Ph*), 4.72-4.68 (1H, m, OCH_2CH(N)Bn), 4.50 (2H, s, CH_2OCH_2Ph), 4.24-4.18 (2H, m, OCH_2CH(N)Bn), 3.96-3.95 (1H, m, $CH_2CH(OH)CH(CH_3)C(O)$), 3.76 (1H, ddd, *J* 14.1 Hz, 7.0 Hz and 2.6 Hz, $CH_2CH(OH)CH(CH_3)C(O)$), 3.48 (2H, t, *J* 6.5 Hz, CH_2OCH_2Ph), 3.25 (1H, dd, *J* 13.4 Hz and 3.3 Hz, one of $OCH_2CH(N)CH_2Ph$), 2.89 (1H, d, *J* 3.0 Hz, OH), 2.79 (1H, dd, *J* 13.4 Hz and 9.5 Hz, $OCH_2CH(N)CH_2Ph$), 1.68-1.55 (4H, m), 1.47-1.41 (2H, m), 1.25 (3H, d, *J* 7.0 Hz, $CH(OH)CH(CH_3)$); δ_C (125MHz, $CDCl_3$) 177.5, 153.0, 138.6, 135.0, 129.4, 129.0, 128.3, 127.6, 127.4, 127.4, 72.9, 71.4, 70.2, 66.2, 55.1, 42.1, 37.8, 33.6, 29.6, 22.7, 10.4.

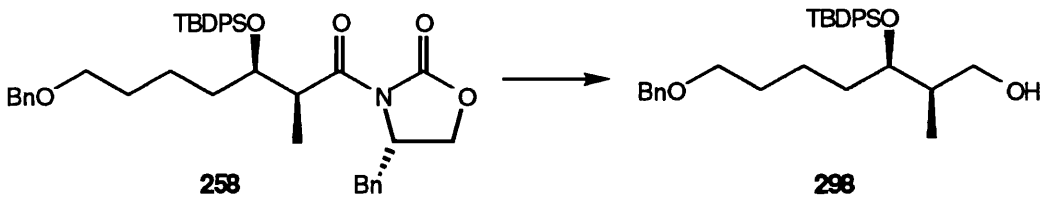
Preparation of (2'*S*, 3'*R*, 4*S*)-4-benzyl-3-[3'-(*tert*-butyldimethylsilyloxy)-2'-methyl-1'-oxaheptyl]-2-oxazolidinone 297



To a stirred solution of alcohol **258** (34.00 g, 80.0 mmol) in DMF (50 ml) was added imidazole (16.31 g, 240.0 mmol), followed by *tert*-butyldiphenylsilyl chloride (35.26 ml, 135.5 mmol). After 1 d, the mixture was partitioned between saturated aqueous NH_4Cl (100 ml) and Et_2O (50 ml). The organics were separated and the aqueous layer extracted with Et_2O (3 x 100 ml). The organics were combined and washed with 2M HCl (1 x 100 ml), H_2O (3 x 200 ml), saturated brine (3 x 200 ml), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual yellow oil was purified by FCC (10-20% Et_2O/petrol)

to give the title compound **297** (47.20 g, 89%) as a clear oil, $[\alpha]_D^{26}$ +38.3 (*c* 0.98 in $CHCl_3$); ν_{max}(film) 2931, 2857, 1780, 1703, 1475, 1454, 1427, 1381, 1351, 1209, 1110, 1046, 1016, 822, 739 and 702 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.69-7.65 (4H, m, Si*Ph*), 7.47-7.22 (16H, m, *Ph*), 4.45 (2H, s, CH_2OCH_2Ph), 4.39-4.33 (1H, m, $CH_2CH(OSi)CH(CH_3)$) 4.21-4.16 (1H, m), 4.06 (1H, dd, *J* 8.8 Hz and 2.0 Hz), 3.90-3.83 (2H, m), 3.36-3.28 (3H, m, CH_2OCH_2Ph and one of $OCH_2CH(N)CH_2Ph$), 2.73 (1H, dd, *J* 13.2 Hz and 9.8 Hz, one of $OCH_2CH(N)CH_2Ph$), 1.64-1.12 (9H, m, includes 1.33 (3H, d, *J* 6.8 Hz,), 1.10 (9H, s, ^tBu); δ_C (100MHz, $CDCl_3$) 174.9 (s), 153.0 (s), 138.6 (s), 136.0 (d), 135.9 (d), 135.5 (s), 134.5 (s), 133.8 (s), 129.7 (d), 129.6 (d), 129.4 (d), 128.9 (d), 128.3 (d), 127.6 (d), 127.5 (d), 127.4 (d), 127.4 (d), 127.3 (d), 73.7 (d), 72.8 (t), 70.1 (t), 65.9 (t), 55.7 (d), 42.4 (d), 37.5 (t), 35.0 (t), 29.5 (t), 27.0 (q), 21.5 (t), 19.4 (s), 10.1 (q); m/z (+FAB) 664 (M+H), 606 (M-^{t}Bu), 586, 408, 323, 199, 183, 135, 117, 91; found: C, 74.3; H, 7.7. $C_{41}H_{49}NO_5Si$ requires C, 74.2; H, 7.4%

Preparation of (2*R*, 3*R*)-7-(benzyloxy)-3-(*tert*-butyldiphenylsilyloxy)-2-methylheptanol 298

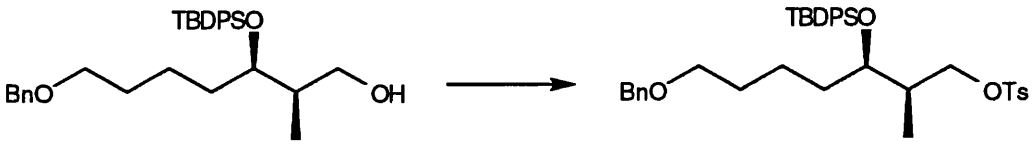


258 **298**

To a cooled (0°C), stirred solution of imide **258** (8.13 g, 12.84 mmol) in THF (40 ml) was added anhydrous MeOH (1.50 ml, 38.52 mmol) followed by $LiBH_4$ (18.35 ml, 2M solution in THF, 38.52 mmol) dropwise over 6 mins. The reaction was then brought to RT. After 1.5h the reaction was poured into a separating funnel containing a saturated solution of Rochelle's salt (50 ml) and then 2M HCl was cautiously added until all the salts had dissolved. The mixture was then extracted with Et_2O (3 x 50 ml), the organics were combined and washed with H_2O (1 x 50 ml), saturated aqueous brine (3 x 50 ml), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual yellow oil was purified by FCC (30% Et_2O/petrol) to give the title compound **298** (5.28 g, 84%) as a clear oil, $[\alpha]_D^{22}$ -27.5 (*c* 0.69 in $CHCl_3$); ν_{max}(film) 3443, 3069, 3048, 2931, 2857, 1589, 1472,

1454, 1427, 1389, 1361, 1110, 1028, 939, 821, 740, 702 and 613 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.72-7.65 (4H, m, Si*Ph*), 7.45-7.25 (11H, m, *Ph*), 4.39 (2H, s, CH_2OCH_2Ph), 3.85-3.79 (1H, m, $CH_2CH(OSi)CH(CH_3)$) 3.65 (1H, t, *J* 9.2 Hz, O*H*), 3.43-3.56 (1H, m), 3.30-3.17 (2H, m), 1.95-1.82 (2H, m), 1.60-1.07 (15H, m, includes 1.05 (9H, s, ^tBu)), 0.83 (3H, d, *J* 6.9 Hz, $CH(OSi)CH(CH_3)$); δ_C (100MHz, $CDCl_3$) 138.6 (s), 136.0 (d), 134.3 (s), 133.7 (s), 129.8 (d), 129.6 (d), 128.3 (d), 127.7 (d), 127.6 (d), 127.5 (d), 77.2 (d), 75.2 (d), 72.8 (t), 70.1 (t), 65.8 (t), 33.1 (t), 29.5 (t), 27.1 (q), 22.5 (t), 19.4 (s), 11.0 (q); m/z (+FAB) 491 (M+H), 433 (M-^{t}Bu), 325, 235, 217, 199, 91; observed: M+H, 491.2985. $C_{31}H_{43}O_3Si$ requires M+H, 491.2981.

Preparation of (2*R*, 3*R*)-7-(benzyloxy)-3-(*tert*-butyldiphenylsilyloxy)-2-methylheptanol *p*-toluenesulfonate 257

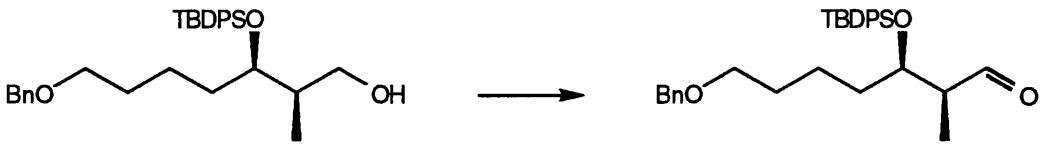


264 **257**

To a stirred solution of alcohol **264** (68 mg, 0.14 mmol) in CH_2Cl_2 (0.3 ml) was added *p*-toluenesulfonyl chloride (40 mg, 0.21 mmol), followed by pyridine (34 µl, 0.42 mmol). After 1 d, the mixture was partitioned between 2M HCl (1 ml) and CH_2Cl_2 (5 ml). The organics were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 5 ml). The organics were combined and washed with 30% aqueous $CuSO_4$ solution (1 x 10 ml), H_2O (3 x 10 ml), saturated brine (3 x 10 ml), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual yellow oil was purified by FCC (30% Et_2O/petrol) to give the title compound **257** (80 mg, 89%) as a clear oil, $[\alpha]_D^{26}$ -5.6 (*c* 0.93 in $CHCl_3$); ν_{max}(film) 3068, 2931, 2857, 1598, 1495, 1455, 1428, 1363, 1189, 1177, 1110, 1044, 968, 816, 741, 703 and 666 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.66 (2H, d, *J* 8.3 Hz, *Ar*), 7.53-7.50 (4H, m, *Ar*), 7.39-7.17 (13H, m, *Ar*), 4.30 (2H, s, CH_2OCH_2Ph), 3.98 (1H, dd, *J* 9.3 Hz and 6.4 Hz), 3.90-3.84 (1H, m), 3.62-3.58 (1H, m, $CH_2CH(OSi)CH(CH_3)$), 3.16-3.08 (2H, m), 2.36 (3H, s, SO_2ArCH_3), 1.88-1.81 (1H, m, $CH_2CH(OSi)CH(CH_3)$), 1.40-0.84 (15H, m,

includes 0.87 (9H, s, ^tBu), 0.81 (3H, d, J 6.9 Hz, CH(OSi)CH(CH_3)); δ_C (100MHz, $CDCl_3$) 145.1 (s), 139.1 (s), 136.5 (d), 135.0 (s), 134.0 (s), 133.7 (s), 130.4 (d), 130.3 (d), 130.1 (d), 128.9 (d), 128.5 (d), 128.2 (d), 128.2 (d), 128.1 (d), 128.0 (d), 77.8 (d), 73.9 (d), 73.8 (t), 73.4 (t), 70.5 (t), 34.1 (t), 29.9 (t), 27.6 (q), 22.8 (t), 22.2 (q), 20.0 (s), 10.9 (q); m/z (+FAB) 643 $(M-H)^+$, 473, 443, 419, 389, 353, 333, 293, 273, 217, 197, 183, 135, 121, 109, 91, 71; found: C, 70.8; H, 7.6. $C_{38}H_{48}O_5SSi$ requires C, 70.8; H, 7.5%.

Preparation of (2*S*, 3*R*)-7-(benzyloxy)-3-(*tert*-butyldiphenylsilyloxy)-2-methylheptanal 266

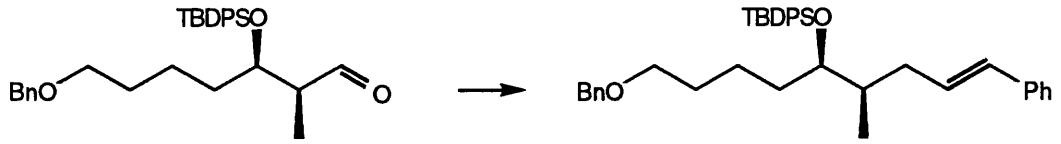


264 **266**

To a stirred solution of alcohol **264** (390 mg, 0.80 mmol) in CH_2Cl_2 (2.6 ml) was added Dess-Martin periodinane reagent (440 mg, 1.04 mmol). After 17 mins sat. aqueous $NaHCO_3$ (25 ml) and Et_2O (25 ml), was added then stirred for 5 mins. The organics were separated and the aqueous extracted with Et_2O (4 x 20 ml). The organics were combined and washed with H_2O (1 x 25 ml), sat. brine (3 x 25 ml), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual yellow oil was purified by FCC (50% Et_2O/petrol) to give the title compound **266** (385 mg, 99%) as a clear oil, $[\alpha]_D^{24}$ +5.1 (c 0.92 in $CHCl_3$); ν_{max}(film) 3069, 2933, 2857, 2709, 1729, 1589, 1472, 1454, 1427, 1390, 1361, 1111, 1027, 1007, 822, 740, 702, 665 and 613 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 9.71 (1H, s, C*H*O), 7.67-7.63 (4H, m, Si*Ph*), 7.43-7.18 (11H, m, *Ph*), 4.38 (2H, s, CH_2OCH_2Ph), 4.22-4.13 (1H, m, CH_2CH(OSi)CH(CH_3), 3.25 (2H, t, J 6.3 Hz, CH_2OCH_2Ph), 2.39 (1H, dq, J 6.9 Hz and 3.0 Hz, CH(OSi)CH(CH_3)CHO), 1.63-1.24 (3H, m), 1.23-1.02 (6H, m, includes 1.09 (3H, d, J 6.8 Hz, CH(OSi)CH(CH_3)), 1.02 (9H, s, ^tBu); δ_C (67.5MHz, $CDCl_3$) 204.9 (s), 138.4 (s), 136.2 (d), 135.9 (d), 135.8 (d), 135.5 (d), 135.5 (d), 134.1 (s), 133.1 (s), 129.8 (d), 129.6 (d), 128.2 (d), 128.0 (d), 127.6 (d), 127.4 (d), 127.4 (d), 127.1 (d), 72.9 (d), 72.7 (t), 69.7 (t), 50.5 (d), 33.9 (t), 29.2 (t), 26.9 (q), 22.2 (t), 19.3 (s), 7.0 (q); m/z (+FAB) 511 (M+Na), 487

(M-H), 431, 373, 339, 325, 283, 263, 239, 233, 223, 205, 199, 183, 161, 145, 135, 121, 105; observed: M+Na, 511.2668. $C_{31}H_{40}NaO_3Si$ requires M+Na, 511.2644.

Preparation of (5*R*, 6*R*, 8*E*)-*O*-benzyl-5-(*tert*-butyldiphenylsilyloxy)-6-methyl-9-phenylnon-8-enol 271



266 **271**

To a suspension of (methoxymethyl)triphenylphosphonium chloride (3.23 g, 9.42 mmol) in Et_2O (30 ml) was added phenyl lithium (5.23 ml, 1.8M solution in cyclohexane/Et_2O, 9.42 mmol). After 15 mins, the contents of the flask were cooled to -78°C before the dropwise addition of a pre-cooled (-78°C) solution of aldehyde **266** (1.83 g, 3.75 mmol) in Et_2O (10 ml) over 25 mins *via* cannula. After 35 mins the mixture was allowed to warm to RT, and stirred for 0.5 h before addition of $HClO_4$ (5 drops , 60% conc.). After *ca.* 15 mins, the mixture was cautiously quenched by addition of saturated aqueous $NaHCO_3$ (10 ml), and the organics were separated. The aqueous layer was extracted with Et_2O (4 x 15 ml), the organics were combined, washed with H_2O (1 x 10 ml), saturated aqueous brine (3 x 10 ml), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The resultant orange oil was taken up in THF (10 ml) and treated with TFA (0.75 ml) and H_2O (2.5 ml). After stirring for 35 mins, the reaction was quenched by cautious addition of sat. aqueous $NaHCO_3$ (15 ml), and diluted with Et_2O (10 ml). The organics were separated and the aqueous layers were extracted with Et_2O (4 x 15 ml). The organics were combined, washed with H_2O (1 x 15 ml), sat. brine (3 x 15 ml), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual orange oil purified by FCC (20% Et_2O/petrol) to give a mixture (1.41 g) of the co-running homologated aldehyde **265** and its corresponding *bis*-methoxy acetal **268** which was used directly in the next step as follows.

Method A from aldehyde 265

To a cooled (0°C), stirred slurry of NaH (142 mg, @95%, 5.61 mmol) in THF (5 ml) containing 15-Crown-5 (0.2 ml, 0.56 mmol) was added a pre-mixed solution of crude aldehyde **265** (1.41 g, *ca.* 2.81 mmol) and diethylbenzylphosphonate (0.88 ml, 4.21 mmol) in THF (15 ml). The reaction was allowed to warm to RT and stirred for a further 1h 20 mins. The contents were then poured into 2M NaOH (10 ml) and extracted with CH_2Cl_2 (4 x 10 ml). The organics were combined and washed with H_2O (1 x10 ml), saturated aqueous brine (3 x 10 ml), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual yellow oil was purified by FCC (20% Et_2O/petrol) to give the title compound **271** (1.139 g, 52%) as a clear oil, $[\alpha]_D^{29}$ +29.0 (*c* 0.94 in $CHCl_3$); ν_{max}(film) 3068, 3026, 2931, 2856, 1589, 1495, 1472, 1454, 1427, 1379, 1361, 1307, 1259, 1189, 1110, 1072, 1028, 966, 939, 821, 740, 702 and 666 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.71-7.50 (4H, m, Ph), 7.42-7.18 (16H, m, Ph), 6.27 (1H, d, *J* 15.8 Hz, $CH_2CHCHPh$), 6.10-5.95 (1H, m, $CH_2CHCHPh$), 4.40 (2H, s, $PhCH_2OCH_2$), 3.70-3.61 (1H, m, $CH_2CH(OSi)CH(CH_3)$, 3.26 (2H, t, *J* 6.5 Hz, $PhCH_2OCH_2$), 2.50-2.38 (1H, m, $CH_2CHCHPh$), 2.12-1.98 (1H, m, $CH_2CHCHPh$), 1.80-1.60 (1H, m, $CH(OSi)CH(CH_3)CH_2$), 1.53-1.00 (15H, m, includes 1.06 (9H, s, *^tBu*), 0.87 (3H, d, *J* 6.9 Hz, $CH(OSi)CH(CH_3)$); δ_C (67.5 MHz, $CDCl_3$) 138.9 (s), 138.1 (s), 136.3 (d), 135.1 (s), 134.6 (s), 131.1 (d), 130.4 (d), 129.7 (d), 129.6 (d), 128.6 (d), 128.5 (d), 127.8 (d), 127.7 (d), 127.6 (d), 127.0 (d), 126.1 (d), 76.5 (d), 73.0 (t), 70.4 (t), 38.0 (d), 36.7 (t), 33.6 (t), 29.8 (t), 27.4 (q), 22.8 (t), 19.8 (s), 14.2 (q); m/z (+FAB) 577 (M+H), 549, 399, 369, 351, 281, 221, 199, 183, 137, 117, 91; found: C, 81.4; H, 8.6. $C_{39}H_{48}O_2Si$ requires C, 81.2; H, 8.4%.

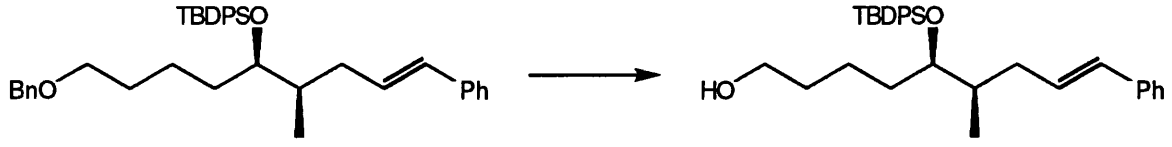
Method B from aldehyde 265

To a stirred suspension of benzyltriphenylphosphonium bromide (84mg, 0.19 mmol) in Et_2O (0.6 ml), was added PhLi (115 µl, 1.8 M solution in cyclohexane:Et_2O, 0.21 mmol) dropwise at RT. After 25 mins, a solution of aldehyde **265** (75 mg, 0.15 mmol) in Et_2O (0.6 ml) was added dropwise *via* cannula over 5 mins. After 1h, the mixture was diluted with Et_2O (20 ml) and filtered, then evaporated under reduced pressure. The residual yellow oil was purified by FCC (20% Et_2O/petrol) to give both the *E/Z* isomers of title compound **271** as a 1.6:1 mixture (83 mg, 97%) as a clear oil.

Method C from aldehyde 265

To a cooled (-78°C), stirred solution of benzylphenyl sulfone (109 mg, 0.47 mmol) in THF (1.0 ml) was added ^{n}BuLi (292 µl, 1.6 M solution in hexanes, 0.47 mmol). After 30 mins a solution of aldehyde **265** (196 mg, 0.39 mmol) in THF (1.0 ml) was added dropwise *via* cannula. After 25 mins, the mixture was partitioned between a saturated aqueous solution of NH_4Cl (10 ml) and CH_2Cl_2 (10 ml). The organics were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 10 ml). The organics were combined, washed with saturated aqueous brine (1 x 10 ml) then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The resulting crude β-hydroxy sulfones were then treated with acetic anhydride (0.1 ml) and pyridine (0.2 ml) for 3h, before partitioning between a saturated aqueous solution of NH_4Cl (10 ml) and CH_2Cl_2 (10 ml). The organics were separated and the aqueous extracted with CH_2Cl_2 (3 x 10 ml). The organics were combined, washed with 2M HCl (1 x 10 ml), H_2O (1 x 10 ml), saturated aqueous $CuSO_4$ (1 x 10 ml), saturated aqueous brine (2 x 10 ml) then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The resultant crude β-acetoxy sulfones were treated with magnesium powder (30 mg, 1.2 mmol) and $HgCl_2$ (catalytic) in anhydrous EtOH (2.0 ml) for 45 mins. The mixture was poured into cold 0.5M HCl (5 ml) and extracted with Et_2O (3 x 10 ml). The organics were combined, washed with H_2O (1 x 10 ml), saturated aqueous $NaHCO_3$ (1 x 10 ml), H_2O (1 x 10 ml), saturated aqueous brine (2 x 10 ml), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual yellow oil was purified by FCC (20% Et_2O/petrol) to give both the *E*/*Z* isomers of title compound **271** as a 2.6:1 mixture (126 mg, 56%) as a clear oil.

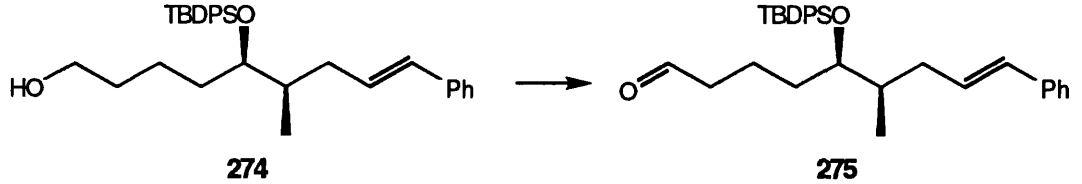
Preparation of (5*R*, 6*R*, 8*E*)-5-(*tert*-butyldiphenylsilyloxy)-6-methyl-9-phenylnon-8-enol 274



271 **274**

To a stirred solution of **271** (56 mg, 0.10 mmol) in CH_2Cl_2 (1.0 ml) was added boron trichloride-dimethyl sulfide complex (315µl, 2M solution in CH_2Cl_2, 0.63 mmol) dropwise over 4 mins. After 1.5 h the mixture was quenched by addition of saturated aqueous $NaHCO_3$ (5 ml) and diluted with CH_2Cl_2 (5.0 ml). The organics were separated and the aqueous layer extracted with CH_2Cl_2 (4 x 5.0 ml). The organics were combined and washed with H_2O (1 x 10 ml), saturated aqueous brine (3 x 10 ml), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual yellow oil was purified by FCC (50% Et_2O/petrol) to give the title compound **274** (45 mg, 95%) as a clear oil, $[\alpha]_D^{31}$ +38.5 (*c* 1.96 in $CHCl_3$); ν_{max}(film) 3353, 3069, 3024, 2932, 2857, 1472, 1457, 1427, 1388, 1361, 1110, 1049, 965, 821, 740, 702, 665 and 612 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.73-7.70 (4H, m, Ph), 7.45-7.41 (2H, m, Ph), 7.38-7.23 (8H, m, Ph), 7.22-7.19 (1H, m, Ph), 6.30 (1H, d, *J* 15.8 Hz, $CH_2CHCHPh$), 6.10-6.03 (1H, m, $CH_2CHCHPh$), 3.71 (1H, dt, *J* 6.3 Hz and 2.7 Hz, $CH_2CH(OSi)CH(CH_3)$, 3.41 (2H, dt, *J* 6.6 Hz and 1.1 Hz, CH_2CH_2OH), 2.52-2.46 (1H, m, $CH_2CHCHPh$), 2.12-2.05 (1H, m, $CH_2CHCHPh$), 1.75-1.70 (1H, m), 1.51-1.36 (2H, m), 1.31-1.22 (2H, m), 1.21-1.08 (11H, m, includes 1.10 (9H, s, ^tBu)), 0.92 (3H, d, *J* 6.8 Hz, $CH(OSi)CH(CH_3)$; δ_C (125MHz, $CDCl_3$) 137.8, 136.1, 136.0, 134.8, 134.3, 130.9, 130.1, 129.5, 129.4, 128.4, 127.5, 127.3, 126.8, 125.9, 76.2, 62.7, 37.9, 36.5, 33.3, 32.5, 27.1, 22.1, 19.6, 14.0; m/z (+FAB) 509 (M+Na), 413, 301, 241, 197, 173, 137, 115, 91; found: C, 79.3; H, 8.9. $C_{32}H_{42}O_2Si$ requires C, 79.0; H, 8.7%.

Preparation of (5*R*, 6*R*, 8*E*)-5-(*tert*-butyldiphenylsilyloxy)-6-methyl-9-phenylnon-8-enal 275

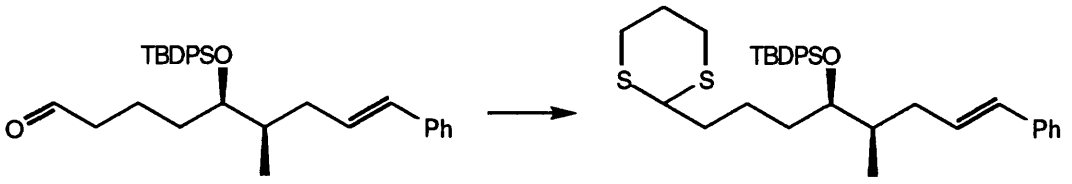


274 **275**

To a stirred solution of alcohol **274** (105 mg, 0.22 mmol) in CH_2Cl_2 (2.1 ml) was added Dess-Martin periodinane reagent (110 mg, 0.26 mmol). After 5 mins "wet" CH_2Cl_2 (0.5 ml) was added and after 15 mins the reaction was concentrated *in vacuo* before the addition of

1:1 solution of saturated aqueous $NaHCO_3$ / 1M $Na_2S_2O_3$ (25 ml) and Et_2O (25 ml), then stirred for 25 mins. The organics were separated and the aqueous extracted with Et_2O (3 x 20 ml). The organics were combined and washed with H_2O (1 x 25 ml), saturated aqueous brine (3 x 25 ml), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual yellow oil was purified by FCC (50% Et_2O/petrol) to give the title compound **275** (98 mg, 94%) as a clear oil, $[\alpha]_D^{27}$ +38.2 (*c* 0.86 in $CHCl_3$); ν_{max}(film) 3070, 3024, 2931, 2856, 2715, 1725, 1589, 1494, 1472, 1461, 1427, 1388, 1361, 1187, 1110, 1072, 966, 938, 821, 740, 702 and 665 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 9.53 (1H, t, *J* 1.4 Hz, C*H*O), 7.70-7.67 (4H, m, Si*Ph*), 7.47-7.04 (11H, m, *Ph*), 6.28 (1H, d, *J* 15.8 Hz, $CH_2CHCHPh$), 6.06-6.00 (1H, m, $CH_2CHCHPh$), 3.70-3.63 (1H, m, $CH_2CH(OSi)CH(CH_3)$, 2.52-2.45 (1H, m), 2.13-2.01 (3H, m), 1.80-1.67 (1H, m), 1.48-1.33 (4H, m), 1.07 (9H, s, ^tBu), 0.88 (3H, d, *J* 6.8 Hz, $CH(OSi)CH(CH_3)$; δ_C (125MHz, $CDCl_3$) 202.3, 137.8, 136.1, 136.0, 131.1, 129.8, 130.0, 129.5, 128.4, 127.5, 127.5, 125.9, 109.6, 75.9, 38.0, 32.9, 27.1, 18.5, 14.1; m/z (+FAB) 485 (M+H), 427 (M-^{t}Bu), 339, 221, 199, 183, 165, 145, 129, 123, 117, 105; observed: M+H, 485.2891. $C_{32}H_{41}O_2Si$ requires M+H, 485.2876

Preparation of (4'*R*, 5'*R*, 7'*E*)-2-[4'-(*tert*-butyldiphenylsilyloxy)-5'-methyl-8'-phenyl-oct-7'-en-1'-yl]-1,3-dithiane 255

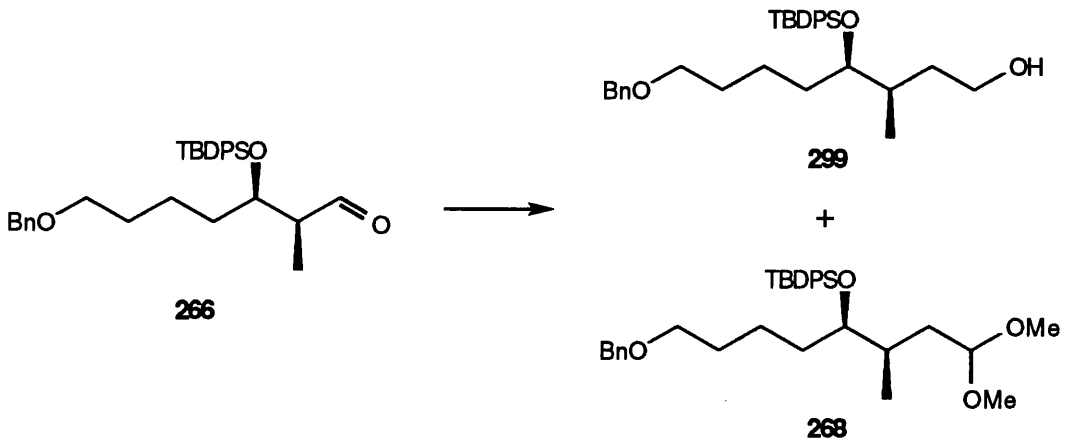


275 **255**

To a stirred solution of aldehyde **275** (76 mg, 0.16 mmol) in CH_2Cl_2 (2.0 ml) was added 1,3-propanedithiol (16 µl, 0.16 mmol) followed by boron trifluoride etherate (4 µl, 0.03 mmol). After 12 h, the reaction was concentrated *in vacuo*. The residual yellow oil was purified by FCC (10% Et_2O/petrol) to give the title compound **255** (90 mg, 100%) as a clear oil, $[\alpha]_D^{25}$ +24.2 (*c* 1.6 in $CHCl_3$); ν_{max}(film) 3069, 3023, 2931, 2895, 2856, 1588, 1493, 1474, 1461, 1426, 1380, 1360, 1275, 1110, 1072, 1051, 1026, 966, 821, 740, 702 and 612

cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.70-7.67 (4H, m, Ph), 7.46-7.40 (2H, m, Ph), 7.39-7.32 (4H, m, Ph), 7.31-7.25 (4H, m, Ph), 7.21-7.16 (1H, m, Ph), 6.27 (1H, d, *J* 15.8 Hz, $CH_2CHCHPh$), 6.08-5.95 (1H, m, $CH_2CHCHPh$), 3.79 (1H, t, *J* 7.0 Hz, $CH_2SCHSCH_2$), 3.70-3.64 (1H, m, $CH_2CH(OSi)CH(CH_3)$, 2.83-2.72 (4H, m), 2.47-2.38 (1H, m, $CH_2CHCHPh$), 2.11-2.02 (2H, m), 1.87-1.77 (1H, m), 1.73-1.63 (1H, m), 1.52-1.41 (3H, m), 1.40-1.20 (3H, m), 1.08 (9H, s, *^tBu*), 0.89 (3H, d, *J* 6.8 Hz, $CH(OSi)CH(CH_3)$; δ_C (125MHz, $CDCl_3$) 137.8 (s), 136.0 (d), 134.8 (s), 130.9 (s), 130.0 (d), 129.5 (s), 129.4 (d), 128.4 (d), 127.5 (d), 127.4 (d), 126.7 (d), 125.9 (d), 76.0 (d), 47.3 (d), 37.6 (d), 36.6 (t), 35.2 (t), 33.2 (t), 30.3 (t), 27.2 (q), 26.0 (t), 22.9 (t), 19.5 (s), 13.8 (q); m/z (+FAB) 573 $(M-H)^+$, 517 (M-^{t}Bu), 319, 281, 221, 199, 135, 117, 91, 73; observed: M^+-^{t}Bu, 517.2101. $C_{31}H_{37}OSiS_2$ requires M^+-^{t}Bu, 517.2055.

Preparation of (3*R*, 4*R*)-8-(benzyloxy)-4-(*tert*-butyldiphenylsilyloxy)-3-methyloctanol 299 and (3*R*, 4*R*)-8-(benzyloxy)-4-(*tert*-butyldiphenylsilyloxy)-3-methyloctanal dimethyl acetal 268



To a suspension of (methoxymethyl)triphenylphosphonium chloride (2.29 g, 6.68 mmol) in Et_2O (25 ml) was added phenyl lithium (3.71 ml, 1.8M solution in cyclohexane/Et_2O, 6.68 mmol). After 15 mins, the contents of the flask were cooled to -78°C before the dropwise addition of a pre-cooled (-78°C) solution of aldehyde **266** (1.30 g, 2.66 mmol) in Et_2O (7 ml) over 20 mins *via* cannula. After 40 mins the mixture was allowed to warm to RT, and stirred for 0.5 h before addition of $HClO_4$ (5 drops, 60% conc.) and the reaction was

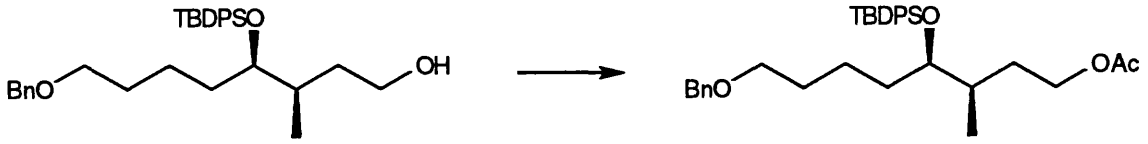
followed closely by tlc. After *ca.* 15 mins, the mixture was cautiously quenched by addition of saturated aqueous $NaHCO_3$ (10 ml), and the organics separated. The aqueous layers were extracted with Et_2O (4 x 10 ml), the organics were combined, washed with H_2O (1 x 10 ml), saturated aqueous brine (3 x 10 ml), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual orange oil was purified by FCC (20% Et_2O/petrol) to give a mixture (0.934 g) of the co-running homologated aldehyde **265** and its corresponding bis-methoxy acetal **268** which was used directly in the next step as follows. To a stirred solution of the impure aldehyde (0.934 g) in MeOH (15 ml) was added $NaBH_4$ (140 mg, 3.720 mmol). After 1h, the reaction was quenched by addition of saturated aqueous NH_4Cl (5 ml) and the bulk of the MeOH removed by concentration *in vacuo*. The aqueous phase was extracted with CH_2Cl_2 (4 x 25 ml). The organics were combined and washed with H_2O (1 x 25 ml), saturated aqueous brine (3 x 25 ml), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual yellow oil was purified by FCC (50% Et_2O/petrol) to give the title compounds **268** (0.225 g, 15%) and **299** (0.652 g, 49%) both as clear oils.

Less polar **268**, $[\alpha]_D^{29}$ -10.5 (*c* 0.90 in $CHCl_3$); ν_{max}(film) 3069, 3047, 2932, 2856, 1472, 1454, 1427, 1388, 1362, 1191, 1110, 1055, 960, 822, 740, 702 and 613 cm^{-1} ; δ_H (500 MHz, $CDCl_3$) 7.70-7.65 (4H, m, Ph), 7.42-7.24 (11H, m, Ph), 4.39 (2H, s, $PhCH_2OCH_2$), 4.30 (1H, t, *J* 5.9 Hz, $CH_3OCHOCH_3$), 3.20-3.28 (8H, m, $PhCH_2OCH_2$ and 2x OCH_3), 1.84 -1.77 (1H, m), 1.76-1.67 (1H, m), 1.52-1.39 (2H, m), 1.37-1.24 (3H, m), 1.13-1.00 (11H, m, includes 1.04 (9H, s, *^tBu*)), 0.89 (3H, d, *J* 6.8 Hz, $CH(OSi)CH(CH_3)CH_2$); δ_C (125MHz, $CDCl_3$) 138.6 (s), 136.0 (d), 136.0 (d), 135.0 (s), 134.1 (s), 129.5 (d), 129.3 (d), 12 8.3 (d), 127.6 (d), 127.5 (d), 127.3 (d), 103.5 (d), 76.7 (d), 72.7 (t), 70.1 (t), 52.7 (q), 52.4 (q), 35.8 (t), 33.6 (t), 33.3 (d), 29.5 (t), 27.1 (q), 22.4 (t), 19.5 (s), 13.9 (q); m/z (+FAB) 547 $(M-H)^+$, 537, 517 ($M-OCH_3$), 503, 485, 459, 445, 427, 409, 395, 383, 369, 353, 299, 261, 239, 197, 135, 91; found: C, 74.8; H, 9.0. $C_{34}H_{48}O_4Si$ requires C, 74.4; H, 8.8%.

More polar **299**, $[\alpha]_D^{29}$ -17.0 (*c* 0.92 in $CHCl_3$); ν_{max}(film) 3415, 3070, 2932, 2857, 1472, 1455, 1427, 1361, 1110, 1050, 822, 739, 702 and 664 cm^{-1} ; δ_H (500 MHz, $CDCl_3$) 7.70-7.65 (4H, m, Ph), 7.44-7.24 (11H, m, Ph), 4.40 (2H, s, $PhCH_2OCH_2$), 3.65-3.57 (2H, m), 3.56-3.47 (1H, m), 3.30-3.22 (2H, m), 1.79-1.67 (2H, m), 1.56 (1H, bs, O*H*), 1.47-1.38 (3H, m), 1.37-1.29 (2H, m), 1.27-1.15 (1H, m), 1.13-1.02 (10H, m, includes 1.05 (9H, s,

^tBu)), 0.89 (3H, d, *J* 6.8 Hz, CH(OSi)CH(CH_3)CH$_2$); δ_C (125MHz, $CDCl_3$) 138.6 (s), 136.0 (d), 134.6 (s), 134.1 (s), 129.6 (d), 129.5 (d), 128.3 (d), 127.6 (d), 127.5 (d), 127.4 (d), 127.3 (d), 77.1 (d), 72.8 (t), 70.1 (t), 61.6 (t), 35.7 (t), 34.7 (d), 33.0 (t), 29.6 (t), 27.1 (q), 22.7 (t), 19.5 (s), 15.0 (q); m/z (+FAB) 505 (M+H), 487 (M-OH), 249, 199, 183, 165, 135, 121, 105, 91, 69; found: C, 75.8; H, 9.1. $C_{32}H_{44}O_3Si$ requires C, 76.1; H, 8.8%.

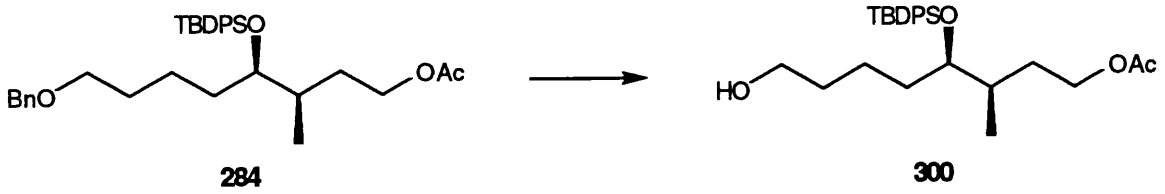
Preparation of (3'*R*, 4'*R*)-[8'-(benzyloxy)-4'-(*tert*-butyldiphenylsilyloxy)-3'-methyloct-1'-yl] acetate 284



299 **284**

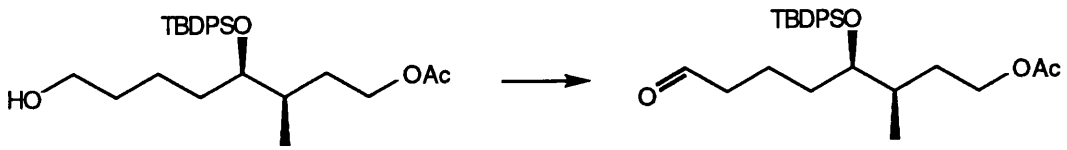
To a stirred solution of alcohol **299** (100 mg, 0.20 mmol) in CH_2Cl_2 (1 ml) was added acetic anhydride (80 µl, 0.85 mmol) followed by pyridine (100 µl, 1.24 mmol). After 15h, the mixture was concentrated *in vacuo* and the residual yellow oil was purified by FCC (50% Et_2O/petrol) to give the title compound **284** (105 mg, 97%) as a clear oil, $[\alpha]_D^{29}$ -4.9 (*c* 0.90 in $CHCl_3$); ν_{max}(film) 3070, 2933, 2857, 1739, 1472, 1455, 1428, 1388, 1364, 1243, 1110, 1044, 822, 740, 702 and 613 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.73-7.69 (4H, m, Ph), 7.47-7.30 (11H, m, Ph), 4.46 (2H, s, PhCH_2OCH_2), 4.10-4.04 (1H, m, CH_2OAc), 4.03-3.97 (1H, m, CH_2OAc), 3.67-3.62 (1H, m, C*H*(OSi)CH(CH$_3$)CH$_2$), 3.35-3.26 (2H, m, PhCH$_2$OCH_2), 2.06 (3H, s, O*Ac*), 1.97-1.88 (1H, m), 1.77-1.68 (1H, m), 1.56-1.07 (16H, m, includes 1.10 (9H, s, ^tBu), 0.90 (3H, d, *J* 6.8 Hz, CH(OSi)CH(CH_3)CH$_2$); δ_C (125MHz, $CDCl_3$) 171.1 (s), 138.6 (s), 136.0 (d), 134.7 (s), 134.1 (s), 129.6 (d), 129.4 (d), 128.3 (d), 127.6 (d), 127.5 m(d), 127.4 (d), 127.3 (d), 76.6 (d), 72.8 (t), 70.1 (t), 63.2 (t), 34.3 (d), 33.0 (t), 31.3 (t), 29.6 (t), 27.1 (q), 22.5 (t), 21.0 (q), 19.5 (s), 14.1 (q); m/z (+FAB) 545 $(M-H)^+$, 517, 485, 471, 439, 429, 339, 323, 291, 261, 241, 221, 199, 181, 161, 135, 91; found: C, 75.0; H, 8.9. $C_{34}H_{46}O_4Si$ requires C, 74.7; H, 8.5%.

Preparation of (3'*R*, 4'*R*)-[4'-(*tert*-butyldiphenylsilyloxy)-8'-hydroxy-3'-methyloct-1'-yl] acetate 300



To a stirred solution of **284** (475 mg, 0.87 mmol) in CH_2Cl_2 (7.0 ml) was added boron trichloride-dimethyl sulfide complex (2.6 ml, 2M solution in CH_2Cl_2, 5.22 mmol) dropwise over 6 mins. After 22 mins, the reaction was cautiously quenched by addition of saturated aqueous $NaHCO_3$ keeping the pH<7. The organics were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 ml). The organics were combined and washed with H_2O (1 x 10 ml), saturated aqueous brine (3 x 10 ml), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual yellow oil was purified by FCC (70% Et_2O/petrol) to give the title compound **300** (363 mg, 92%) as a clear oil, $[\alpha]_D^{27}$ -1.7 (*c* 0.90 in $CHCl_3$); ν_{max}(film) 3434, 3070, 3047, 2933, 2858, 1740, 1472, 1462, 1427, 1389, 1365, 1244, 1110, 1044, 822, 741, 703, 688 and 614 cm^{-1} ; δ_H (500 MHz, $CDCl_3$) 7.70-7.63 (4H, m, Ph), 7.46-7.32 (6H, m, Ph), 4.08-4.02 (1H, m, C*H*$_2$OAc), 4.00-3.93 (1H, m, C*H*$_2$OAc), 3.60 (1H, dt, *J* 6.2 Hz and 2.8 Hz, C*H*(OSi)CH(CH_3)CH_2), 3.40 (2H, t, *J* 6.3 Hz), 2.02 (3H, s, O*Ac*), 1.93-1.85 (1H, m), 1.74-1.65 (1H, m), 1.53-1.07 (7H, m), 1.05 (9H, s, ^tBu), 0.87 (3H, d, *J* 6.9 Hz, CH(OSi)CH(C*H*$_3$)CH_2); δ_C (125MHz, $CDCl_3$) 171.2 (s), 136.0 (d), 136.0 (d), 134.8 (s), 134.1 (s), 129.6 (d), 129.4 (d), 127.5 (d), 127.4 (d), 76.5 (d), 63.2 (t), 62.7 (t), 34.4 (d), 32.9 (t), 32.5 (t), 31.4 (t), 27.1 (q), 22.0 (t), 21.0 (q), 19.5 (s), 14.2 (q); m/z (+FAB) 457 (M+H), 439, 395, 381, 369, 323, 241, 221, 199, 161, 135, 81; found: C, 71.2; H, 9.0. $C_{27}H_{40}O_4Si$ requires C, 71.0; H, 8.8%.

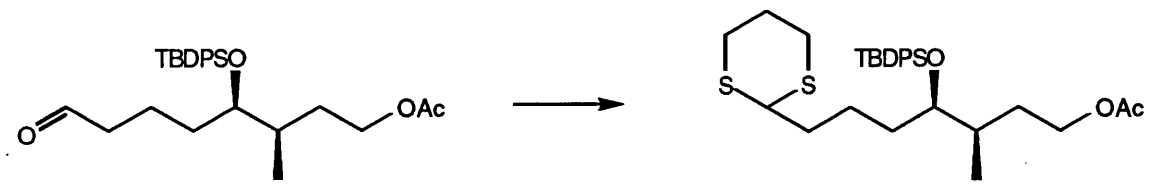
Preparation of (3'*R*, 4'*R*)-[4'-(*tert*-butyldiphenylsilyloxy)-3'-methyl-8'-oxa-oct-1'-yl] acetate 301`



300 **301**

To a stirred solution of alcohol **300** (274 mg, 0.60 mmol) in CH_2Cl_2 (8.0 ml) was added Dess-Martin periodinane reagent (331 mg, 0.78 mmol). After 11 mins H_2O (1 drop) was added and after a further 35 mins the reaction was concentrated *in vacuo* before the addition of 1:1 solution of saturated aqueous $NaHCO_3$ / 1M $Na_2S_2O_3$ (25 ml) and Et_2O (25 ml). The mixture was stirred for 30 mins. The organics were separated and the aqueous layer extracted with Et_2O (3 x 20 ml). The organics were combined and washed with H_2O (1 x 25 ml), saturated aqueous brine (3 x 25 ml), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual yellow oil was purified by FCC (30% Et_2O/petrol) to give the title compound **301** (251 mg, 92%) as a clear oil, $[\alpha]_D^{29}$ -1.5 (*c* 0.90 in $CHCl_3$); ν_{max}(film) 3070, 3048, 2958, 2932, 2857, 2715, 1739, 1472, 1462, 1427, 138 8, 1365, 1243, 1110, 1043, 822, 741, 703, 688 and 613cm^{-1}; δ_H (500 MHz, $CDCl_3$) 9.52 (1H, t, J 1.5 Hz, C*H*O), 7.70-7.64 (4H, m, Ph), 7.45-7.32 (6H, m, Ph), 4.09-4.01 (1H, m, C*H*$_2$OAc), 4.00-3.93 (1H, m, C*H*$_2$OAc), 3.61-3.56 (1H, m, C*H*(OSi)CH(CH_3)CH_2), 2.10-2.05 (2H, m C*H*$_2$CHO), 2.02 (3H, s, O*Ac*), 1.95-1.87 (1H, m), 1.75-1.67 (1H, m), 1.50-1.28 (5H, m), 1.05 (9H, s, ^{t}*Bu*), 0.86 (3H, d, *J* 6.8 Hz, CH(OSi)CH(C*H*$_3$)CH_2); δ_C (125MHz, $CDCl_3$) 202.2 (s), 171.1 (s), 136.0 (d), 135.9 (d), 134.5 (s), 133.9 (s), 129.7 (d), 129.6 (d), 127.6 (d), 127.5 (d), 76.2 (d), 63.1 (t), 43.5 (t), 34.5 (d), 32.5 (t), 31.1 (t), 27.1 (q), 21.0 (q), 19.5 (s), 18.5 (t), 14.3 (q); m/z (+FAB) 477 (M+Na), 455 (M+H), 397 (M-^{t}Bu), 337, 323, 241, 221, 199, 181, 165, 149, 140, 121, 111; observed: M+H, 455.2600. $C_{27}H_{39}O_4Si$ requires M+H, 455.2618.

Preparation of (3'*R*, 4'*R*)-[4'-(*tert*-butyldiphenylsilyloxy)-7'-(1'',3''-dithan-2''-yl))-3'-methyl-heptyl] acetate 285



301 **285**

To a stirred solution of aldehyde **301** (89 mg, 0.20 mmol) in CH_2Cl_2 (1.0 ml) was added 1,3-propanedithiol (19 µl, 0.20 mmol) followed by boron trifluoride etherate (5 µl, 0.04 mmol). After 16 h, the reaction was concentrated *in vacuo*. The residual yellow oil was purified by FCC (30% Et_2O/petrol) to give the title compound **285** (93 mg, 87%) as a clear oil, $[\alpha]_D^{27}$ -12.4 (*c* 0.95 in $CHCl_3$); ν_{max}(film) 3069, 3047, 2932, 2895, 2856, 1739, 1472, 1461, 1427, 1388, 1364, 1242, 1110, 1044, 822, 741, 703, 688 and 613 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.70-7.65 (4H, m, SiPh), 7.45-7.35 (6H, m, SiPh), 4.05-3.98 (1H, m, C*H*$_2$OAc), 3.97-3.91 (1H, m, C*H*$_2$OAc), 3.78 (1H, t, *J* 7.0 Hz, $CH_2SCHSCH_2$), 3.58 (1H, dt, *J* 5.9 Hz and 2.8 Hz, C*H*(OSi)CH(CH_3)CH_2), 2.82-2.72 (4H, m), 2.11-2.04 (1H, m), 2.01 (3H, s, OA*c*), 1.89-1.77 (2H, m), 1.71-1.62 (1H, m, CH(OSi)C*H*(CH_3)CH_2), 1.52-1.39 (4H, m), 1.38-1.18 (4H, m), 1.05 (9H, s, ^tBu), 0.86 (3H, d, *J* 6.8 Hz, CH(OSi)CH(C*H*$_3$)CH_2); m/z (+FAB) 543 $(M-H)^+$, 487, (M-^{t}Bu), 467, 445, 429, 409, 367, 323, 289, 271, 241, 199, 181, 155, 95, 75; found: C, 66.2; H, 8.5. $C_{30}H_{44}O_3S_2Si$ requires C, 66.1; H, 8.1%.

Preparation of (4'*R*, 5'*R*)-2-[4'-(*tert*-butyldiphenylsilyloxy)-7'-hydroxy-5'-methylheptyl]-1,3-dithiane 286

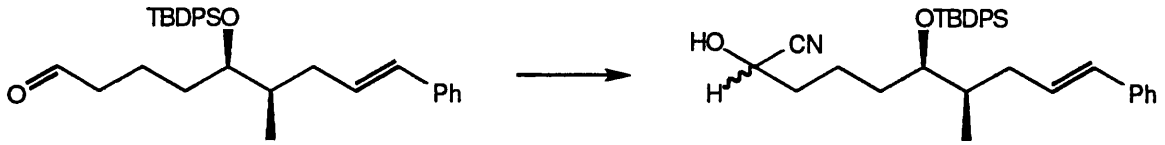
285 286

To a stirred solution of acetate **285** (205 mg, 0.38 mmol) in MeOH (1.5 ml) was added K_2CO_3 (104 mg, 0.76 mmol). After 1h, the mixture was filtered and concentrated *in vacuo*. The residual yellow oil was purified by FCC (loaded with 30% Et_2O/petrol containing MeOH (100 μl) to complete dissolution, then developed and eluted with 30% Et_2O/petrol) to give the title compound **286** (186 mg, 98%) as a clear oil, $[\alpha]_D^{29}$ -21.0 (*c* 0.90 in $CHCl_3$); ν_{max}(film) 3437, 3069, 3047, 2932, 2894, 2856, 1472, 1461, 1427, 1381, 1110, 1054, 1006, 822, 741, 703, 688 and 614 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.65-7.55 (4H, m, Si*Ph*), 7.40-7.26 (6H, m, Si*Ph*), 3.70 (1H, t, *J* 6.9 Hz, CH_2S $CHSCH_2$), 3.58-3.37 (3H, m, CH(OSi)$CH(CH_3)CH_2$ and CH_2OH), 2.74-2.63 (4H, m), 2.05-1.95 (1H, m), 1.84-1.06 (20H, m), 0.99 (9H, s, ^tBu), 0.77 (3H, d, *J* 6.9 Hz, CH(OSi)$CH(CH_3)CH_2$); δ_C (67.5 MHz, $CDCl_3$) 136.0 (d), 134.5 (s), 134.0 (s), 129.6 (d), 129.5 (d), 127.5 (d), 127.4 (d), 76.7 (d), 61.4 (t), 47.2 (d), 35.9 (t), 35.1 (t), 34.3 (d), 32.9 (t), 30.2 (t), 30.2 (t), 27.1 (q), 26.0 (t), 23.0 (t), 19.5 (s), 14.7 (q); m/z (+FAB) 503 (M+H), 501 $(M-H)^+$, 445, 367, 295, 247, 229, 213, 199, 183, 154, 135, 121, 95, 69; found: C, 66.9; H, 8.8. $C_{28}H_{42}O_2S_2Si$ requires C, 66.9; H, 8.4%.

Miscellaneous Experimental

The following section contains experimental details for some of the compounds that deviate from the main synthetic route. They have not been fully characterised as they were generated as stereoisomeric mixtures, and hence difficult to characterise. They are included here as a reference for future workers.

Preparation of cyanohydrin 279



275 **279**

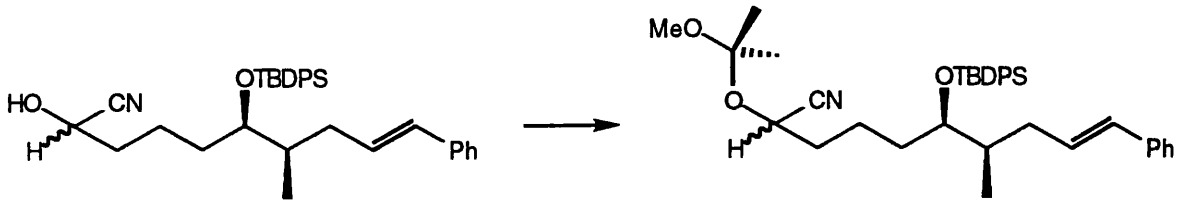
To a cooled (0°C), stirred solution of aldehyde **275** (271 mg, 0.56 mmol) in CH_2Cl_2 (0.8 ml) containing zinc iodide (1 mg, catalytic amount) was added trimethylsilyl cyanide (115 µl, 0.86 mmol). The reaction was allowed to warm to RT. After 0.5 h, THF (200 µl), TFA (200 µl) and H_2O (200 µl) were added and the mixture was stirred for 10 minutes. The mixture was then neutralised by addition of saturated aqueous $NaHCO_3$ and diluted with CH_2Cl_2 (5.0 ml). The organics were separated and the aqueous extracted with CH_2Cl_2 (4 x 5 ml). The organics were combined and washed with H_2O (1 x 10 ml), saturated aqueous brine (3 x 10 ml), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual yellow oil was purified by FCC (30% Et_2O/petrol) to give a 1:1 mixture of inseparable diastereoisomers **279** (250 mg, 88%) as a clear oil, ν_{max}(film) 3444, 3070, 3024, 2956, 2931, 2891, 2857, 2247, 1652, 1589, 1494, 1472, 1461, 1427, 1389, 1361, 1110, 1072, 966, 821, 741, 703 and 613 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.72-7.60 (8H, m, Ph), 7.47-7.15 (22H, m, Ph), 6.30 (2H, d, *J* 15.8 Hz, $CH_2CHCHPh$), 6.12-5.99 (2H, m, $CH_2CHCHPh$), 4.16-4.03 (2H, m, $HOCH(CN)CH_2$), 3.72-3.62 (2H, m, $CH_2CH(OSi)CH(CH_3)$), 2.56-2.43 (2H, m, $CH_2CHCHPh$), 2.13-2.00 (2H, m, $CH_2CHCHPh$), 1.94-1.82 (2H, m), 1.80-1.64 (2H, m, $CH_2CH(OSi)CH(CH_3)$), 1.53-1.12 (10H, m), 1.08 (18H, s, *^tBu*), 0.96-0.80 (3H, m, $CH(OSi)CH(CH_3)$).

Preparation of ethoxyethyl protected cyanohydrin 277

279 **277**

To a cooled (0°C), stirred solution of cyanohydrin **279** (250 mg, 0.49 mmol) in CH_2Cl_2 (2.0 ml) containing pyridinium *p*-toluenesulfonate (catalytic amount) was added ethyl vinyl ether (94 µl, 0.98 mmol). The reaction was allowed to warm to RT and stirred for 2 h after which time more pyridinium *p*-toluenesulfonate (catalytic amount) and ethyl vinyl ether (94 µl, 0.98 mmol) were added. After 3 h, finely powdered K_2CO_3 (10 mg) was added. After 10 h, the reaction was diluted with CH_2Cl_2 (5 ml) and washed with saturated aqueous $NaHCO_3$ (1 x 5 ml), H_2O (1 x 5 ml), saturated aqueous brine (3 x 5 ml), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual yellow oil was purified by FCC (10% Et_2O/petrol) to give a 1:1:1:1 mixture of diastereoisomers **277** (239 mg, 84%) as a clear oil, δ_H (500 MHz, $CDCl_3$) 7.74-7.61 (16H, m, Ph), 7.45-7.38 (8H, m, Ph), 7.37-7.30 (16H, m, Ph), 7.29-7.20 (16H, m, Ph), 7.19-7.13 (4H, m, Ph), 6.29 (4H, d, *J* 15.8 Hz, $CH_2CHCHPh$), 6.08-5.98 (4H, m, $CH_2CHCHPh$), 4.86-4.80 (2H, m, $EtOCH(CH_3)OCH(CN)$), 4.73-4.66 (2H, m, $EtOCH(CH_3)OCH(CN)$), 4.24 (1H, t, *J* 6.5 Hz, $EEOCH(CN)CH_2$), 4.18 (1H, t, *J* 6.5 Hz, $EEOCH(CN)CH_2$), 4.00 (1H, t, *J* 6.5 Hz, $EEOCH(CN)CH_2$), 3.96 (1H, t, *J* 6.5 Hz, $EEOCH(CN)CH_2$), 3.72-3.64 (4H, m), 3.63-3.55 (4H, m), 3.53-3.37 (4H, m), 2.52-2.41 (4H, m, $CH_2CHCHPh$), 2.10-1.97 (4H, m, $CH_2CHCHPh$), 1.77-1.65 (4H, m, $CH(OSi)CH(CH_3)CH_2$), 1.60-1.10 (48H, m), 1.09-1.06 (36H, m, ^tBu), 0.91-0.82 (12H, m, $CH(OSi)CH(CH_3)CH_2$.

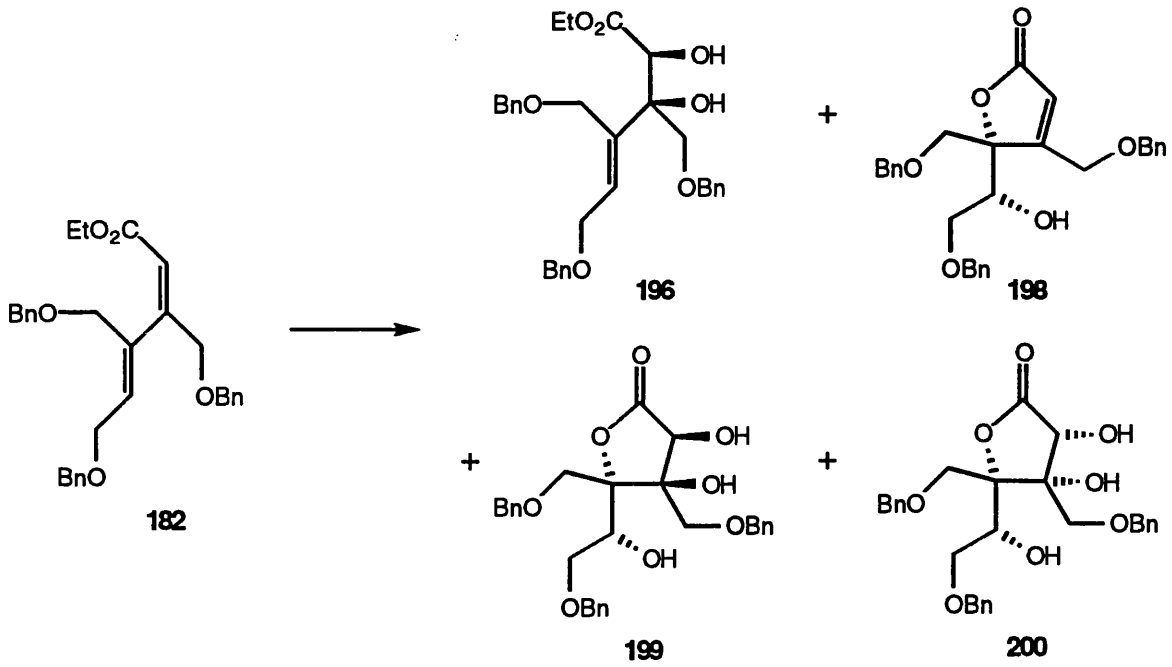
Preparation of methoxy version of cyanohydrin 278



279 **278**

Cyanohydrin **279** (80 mg, 0.16 mmol) was treated with *p*-TsOH (catalytic amount) followed by 2-methoxypropene (0.9 ml). After 5 mins, finely powdered K_2CO_3 (10 mg) was added and after 5 mins, triethylamine (0.1 ml) was added. The mixture was concentrated *in vacuo* and the residual yellow oil was purified by FCC (10% Et_2O/petrol) to give a 1:1 mixture of diastereoisomers (73 mg, 82%) as a clear oil, δ_H (270 MHz, $CDCl_3$) 7.74-7.63 (8H, m, Ph), 7.47-7.15 (22H, m, Ph), 6.29 (2H, d, *J* 15.5 Hz, $CH_2CHCHPh$), 6.10-5.98 (2H, m, $CH_2CHCHPh$), 4.21 (1H, t, *J* 6.3 Hz, -$OCH(CN)CH_2$), 4.12 (1H, t, *J* 6.3 Hz, -$OCH(CN)CH_2$), 3.71-3.62 (2H, m, $CH(OSi)CH(CH_3)CH_2$), 3.16 (3H, s, OCH_3), 3.15 (3H, s, OCH_3), 2.55-2.42 (2H, m, $CH_2CHCHPh$), 2.11-1.98 (2H, m, $CH_2CHCHPh$), 1.80-1.60 (2H, m, $CH(OSi)CH(CH_3)CH_2$), 1.50-1.10 (24H, m), 1.08 (18H, s, *^tBu*), 0.89 (3H, d, *J* 6.9 Hz, $CH(OSi)CH(CH_3)CH_2$) 0.88 (3H, d, *J* 6.9 Hz, $CH(OSi)CH(CH_3)CH_2$).

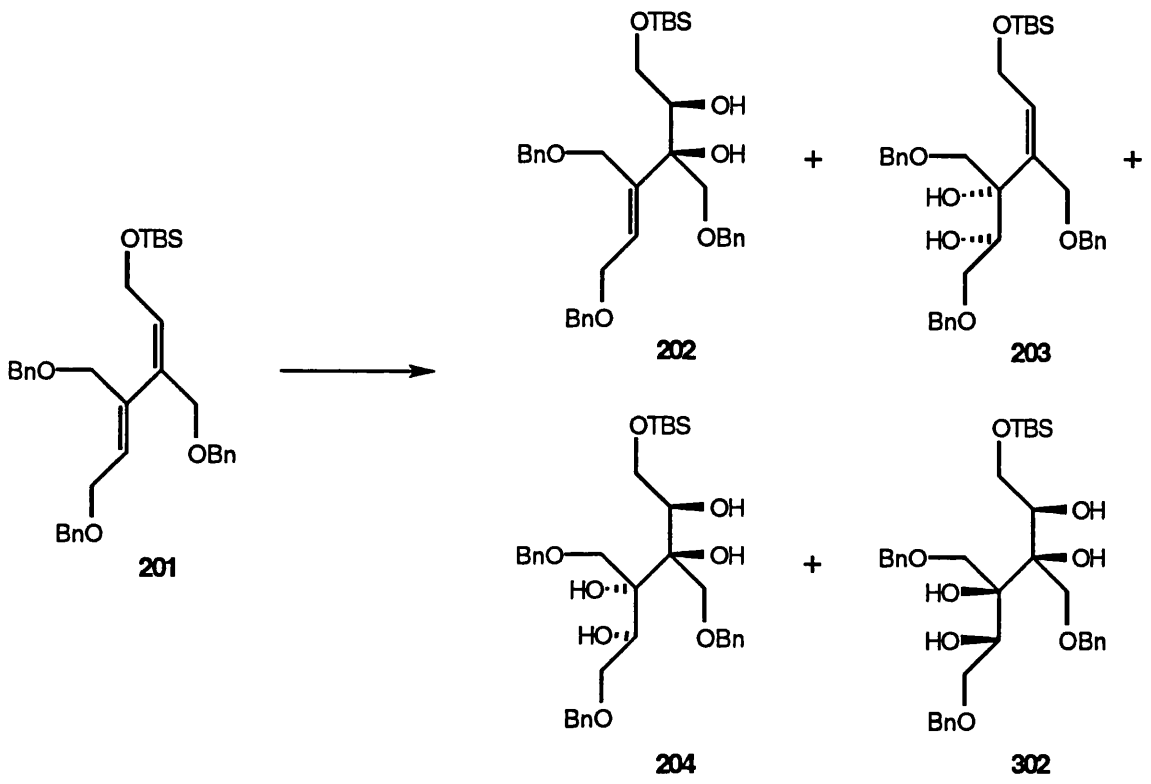
Synthesis of the butenolide 198, the diol 196, and the triols 199 and 200.



To a vigorously stirred solution of diene **182** (0.50 g, 1.03 mmol) in ^{t}BuOH (1.5 ml) and H_2O (1.5 ml) was added AD-mix-β (1.44 g) followed by $K_2S_2O_8$ (278 mg, 1.03 mmol), $(DHQD)_2$-PHAL (32 mg, 0.04 mmol), OsO_4 (catalytic) and $CH_3SO_2NH_2$ (196 mg, 2.06 mmol). After 2d, solid Na_2SO_3 (1.5 g) and EtOAc were added and the mixture was stirred for 3h, then filtered and the solid residues re-extracted with EtOAc (x4). The filtrate and EtOAc extracts were combined, then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by FCC (95% Et_2O/CH_2Cl_2, then increasing the polarity to 100% Et_2O then 20% MeOH/EtOAc). The first compound eluted was the butenolide **198** (70 mg, 13%), δ_H(270 MHz, $CDCl_3$) 7.32-7.20 (15H, m, Ph), 6.10 (1H, s, C*H*=), 4.75-4.0 (9H, m, 6x Ph*CH*$_2$OCH$_2$, PhCH$_2$O*CH*$_2$, PhCH$_2$OCH$_2$*CH*OH), 3.76 (1H, d, *J* 10.6 Hz, PhCH$_2$O*CH*$_2$), 3.70 (1H, d, *J* 10.6 Hz, PhCH$_2$O*CH*$_2$), 3.62-3.54 (1H, m, PhCH$_2$O*CH*$_2$CHOH), 3.42-3.34 (1 H, m, PhCH$_2$O*CH*$_2$CHOH), 2.93 (1 H, d, *J* 4.8 Hz, O*H*); δ_C(100 MHz, $CDCl_3$) 171.4 (s), 169.2 (s), 137.3 (s), 137.23 (s), 137.20 (s), 128.5 (d), 128.0 (d), 127.92 (d), 127.87 (d), 127.7 (d), 127.6 (d), 127.0 (d), 117.5 (d), 89.8 (s), 73.8 (t), 73.6 (t), 73.2 (t), 70.5 (t), 70.1 (d), 69.1 (t), 66.1 (t), followed by the diol **196** (117 mg, 22%), δ_H(270 MHz, $CDCl_3$) 7.32-7.20 (15H, m, Ph), 5.98 (1H, t, *J* 6.2 Hz, C*H*=), 4.48-4.38 (7H, m, includes 4.48 (2H, s, Ph*CH*$_2$OCH$_2$), 4.43 (2H, s, Ph*CH*$_2$OCH$_2$) and 4.40 (2H, s,

PhC*H*$_2$OCH$_2$)), 4.28 (1H, s, C*H*OH or 3° O*H*), 4.14-3.91 (6H, m, 2x PhCH$_2$OC*H*$_2$, CO$_2$C*H*$_2$CH$_3$), 3.81-3.41 (3H, m, *i*ncludes 3.81 (1H, d, *J* 9.3 Hz, PhCH$_2$OC*H*$_2$), 3.65 (1H, d, *J* 9.3 Hz, PhCH$_2$OC*H*$_2$)), 1.12 (3H, t, *J* 7.0 Hz, CO$_2$CH$_2$C*H*$_3$); δ_C(67.5 MHz, $CDCl_3$) 172.0 (s), 138.0 (s), 137.6 (s), 137.5 (s), 130.2, 128.22, 128.18, 127.7, 127.63, 127.58, 127.4, 76.5 (s), 73.7 (d), 73.5 (t), 72.4 (t), 72.1 (t), 66.1 (t), 64.8 (t), 61.2 (t), 13.8 (q), and then the triols **199** and **200** as a mixture.

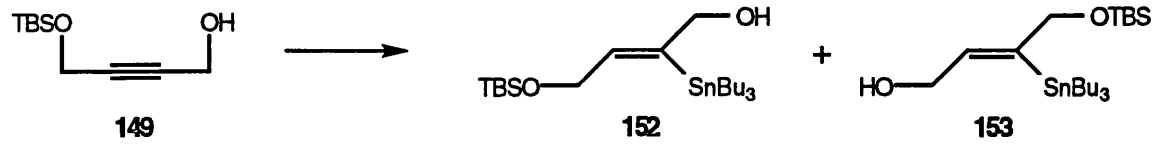
Preparation of diols 202, 203, and tetraols 204 and 302.



To a vigourously stirred solution of diene **201** (0.622 g, 1.1 mmol) in ^{t}BuOH (1.5 ml) and H_2O (1.5 ml) was added AD-mix-β (1.44 g) followed by $K_2S_2O_8$ (594 mg, 2.2 mmol,), $(DHQD)_2$-PHAL (32 mg, 0.04 mmol), $K_2OsO_2(OH)_4$ (catalytic) and $CH_3SO_2NH_2$ (196 mg, 2.06 mmol). After 7d, solid Na_2SO_3 (1.5 g) and EtOAc were added and the mixture stirred for 3h, then filtered and the solid residues re-extracted with EtOAc (x4). The filtrate and EtOAc extracts were combined and dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by FCC (50% Et_2O/petrol) to give an inseparable mixture

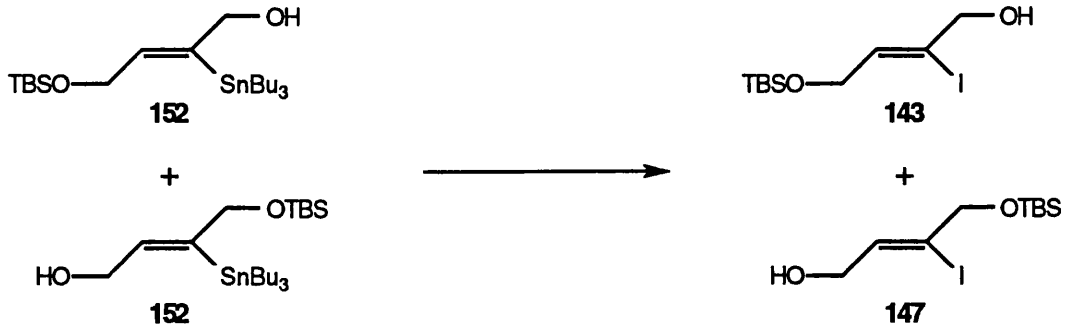
of the diols **202** and **203** (190 mg total) and an inseparable mixture of the tetrols **204** and **302** (57 mg, 8%) all as clear oils.

Synthesis of the vinyl stannanes 152 and 153



A mixture of tributyltin hydride (263 µl, 0.98 mmol), propargylic alcohol **149** (200 mg, 0.98 mmol), and AIBN (1.6 mg, 0.01 mmol) were heated at 85°C under N_2 for 1h 15mins and then allowed to cool to RT. The mixture was purified by loading directly onto silica gel (10% Et_2O/petrol) to give the two title compounds **152** and **153** (405 mg, 89%) as an inseparable mixture, ν_{max}(film)/cm^{-1} 3357, 2956, 2879, 2855, 1463, 1397, 1376, 1253, 1088, 1004, 836, 776 and 665; δ_H(400 MHz, $CDCl_3$) 6.46-6.42 (1H, m, C*H*=), 6.36-6.42 (1H, m, C*H*=), 4.28-4.20 (4H, m, CH_2), 4.15-4.07 (4H, m, CH_2), 1.60-1.30 (36H, m, CH_2), 0.90-0.75 (36H, m, CH_3, ^{t}Bu); δ_C(100 MHz, $CDCl_3$) 145.5 (s), 140.0 (d), 136.5 (d), 70.2 (t), 69.9 (t), 65.4 (t), 64.9 (t), 29.5 (t), 27.7 (t), 26.3 (s), 23.0 (s), 18.8 (s), 14.0 (q), 10.8 (t), 10.6 (t).

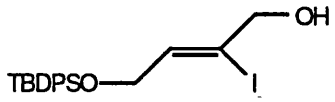
Synthesis of the vinyl iodides 143 and 147 from their corresponding vinyl stannanes.



To a cooled (4°C), stirred solution of the stannanes **152** and **153** (249 mg, 0.54 mmol, as a 1:1 mixture of isomers) in CCl_4 (4 ml) was added a pre-cooled (0°C) solution of iodine (410 mg, 1.61 mmol) in CCl_4 (6 ml), dropwise *via* cannula. After 8 mins a saturated aqueous

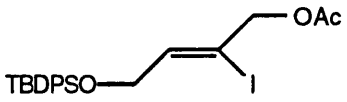
solution of sodium thiosulfate (5 ml) was added and then the mixture was extracted with Et_2O (3 x 10 ml). The organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by FCC (10% Et_2O/petrol) to give the title compounds **143** and **147** (176 mg, 100%). Spectral data as synthesised previously.

Miscellaneous data



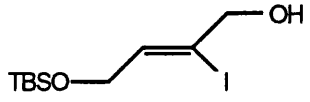
145

δ_H(270 MHz, $CDCl_3$) 7.75-7.67 (5H, m, Ph), 7.48-7.37 (5H, m, Ph), 6.23 (1H, tt, *J* 5.1 Hz and 1.5 Hz, CH_2CH=), 4.32 (2H, dt, *J* 5.3 Hz and 1.3 Hz, $SiOCH_2CH$=), 4.19 (2H, d, *J* 1.3 Hz, CH=C(I)CH_2OH), 1.85 (1H, bs, O*H*), 1.07 (9H, s, ^tBu).



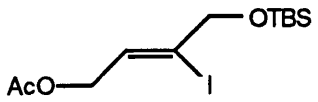
146

δ_H(270 MHz, $CDCl_3$) 7.68-7.65 (5H, m, Ph), 7.47-7.36 (5H, m, Ph), 6.26 (1H, t, *J* 5.1, CH_2CH=), 4.72 (2H, s, CH_2OAc), 4.30 (2H, d, *J* 5.1 Hz with further splitting, $SiOCH_2CH$=), 2.12 (3H, s, CH_3CO), 1.06 (9H, s, ^tBu).



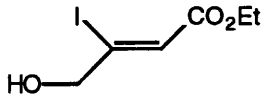
143

δ_H (270 MHz, $CDCl_3$) 6.17 (1H, tt, *J* 5.0 Hz and 1.3 Hz, C*H*=), 4.27 (2H, t, *J* 1.3 Hz, HC=C(I)CH_2OH), 4.25-4.23(2H, m, $SiOCH_2CH$=), 1.97(1H, bs, O*H*), 0.90 (9H, s, ^tBu), 0.09 (6H, s, Me_2Si); δ_C(100 MHz, $CDCl_3$) 135.7 (d), 105.6 (s), 71.2 (t), 67.6 (t), 25.9 (s), 18.28 (q).



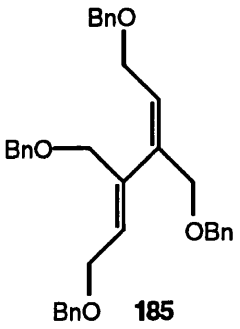
148

δ_H(400 MHz, $CDCl_3$) 6.26-6.22 (1H, m, C*H*=), 4.70-4.68 (2H, d, CH_2OAc), 4.27-4.25 (2H, s, CH_2OSi), 2.08 (3H, s, CH_3CO), 0.92 (9H, s, ^tBu), 0.10 (6H, s, Me_2Si).



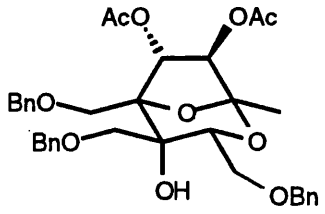
160

δ_H(270 MHz, $CDCl_3$) 6.80 (1H, t, *J* 1.8 Hz, C*H*=), 4.36 (2H, dd, *J* 4.8 Hz and 1.3 Hz, CH_2OH), 4.23 (2H, q, *J* 7.1 Hz, $CO_2CH_2CH_3$), 2.58 (1H, t, *J* 4.8 Hz, O*H*), 1.30 (3H, t, *J* 7.1 Hz, $CO_2CH_2CH_3$).



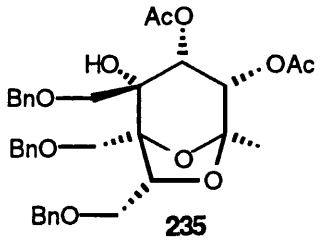
185

δ_H (270 MHz, $CDCl_3$) 7.36-7.22 (20H, m, Ph), 5.86 (1H, t, *J* 6.3 Hz, C*H*=), 5.67 (1H, t, *J* 6.4 Hz, C*H*=), 4.47 (2H, s, $PhCH_2O$),4.454 (2H, s, $PhCH_2O$), 4.450 (2H, s, $PhCH_2O$), 4.37 (2H, s, $PhCH_2O$), 4.20 (2H, d, *J* 6.4 Hz, $PhCH_2OCH_2$), 4.12-4.07 (4H, m, 2x $PhCH_2OCH_2$), 4.07 (2H, s, $PhCH_2OCH_2$); δ_C(100 MHz, $CDCl_3$) 141.5 (s), 138.3 (s), 138.2 (s), 138.1 (s), 138.0 (s), 136.7 (s), 136.6 (s), 131.1 (d), 128.6 (d), 128.5 (d), 128.4 (d), 128.3 (d), 128.2 (d), 128.1 (d), 127.9 (d), 127.7 (d), 127.6 (d), 127.5 (d), 127.1 (d), 72.8 (t), 72.3 (t),72.1 (t), 71.8 (t), 67.1 (t), 66.4 (t), 65.8 (t).



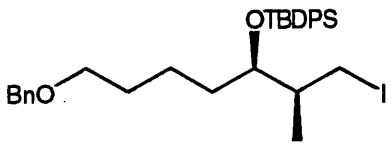
231

δ_H (270 MHz, $CDCl_3$) 7.40 -7.18 (15H, m, *Ph)*, 6.01 (1H, d, *J* 2.8 Hz, *H*6), 5.11 (1H, d, *J* 2.8 Hz, *H*7), 4.57 (1H, d, *J* 12.1 Hz, one of $PhCH_2OCH_2$), 4.51 (1H, d, *J* 12.1 Hz, $PhCH_2OCH_2$), 4.48-4.29 (5H, m, includes, 4.43 (1H, t, *J* 4.6 Hz, *H*3), 4.19 (1H, s, 4-O*H*), 3.84 (1H, dd, *J* 11.1 Hz and 3.8 Hz, $PhCH_2OCH_2$), 3.82 (1H, d, *J* 10.1 Hz, $PhCH_2OCH_2$), 3.69-3.58 (3H, m, $PhCH_2OCH_2$), 3.54 (1H, d, *J* 10.1 Hz, $PhCH_2OCH_2$), 2.15 (3H, s, O*Ac*), 2.05 (3H, s, O*Ac*), 1.54 (3H, s, C1'-CH_3); δ_C (100MHz, $CDCl_3$) 170.0 (s), 169.5 (s), 138.2 (s), 137.6 (s), 137.0 (s), 128.4 (d), 128.3 (d), 128.3 (d), 128.0 (d), 127.7 (d), 127.7 (d), 127.6 (d), 127.6 (d), 103.5 (s), 85.0 (s), 81.2 (d), 77.7 (d), 74.1 (t), 73.5 (t), 73.1 (d), 73.0 (t), 71.7 (s), 70.0 (t), 69.3 (t), 22.6 (q), 20.9 (q), 20.7 (q).



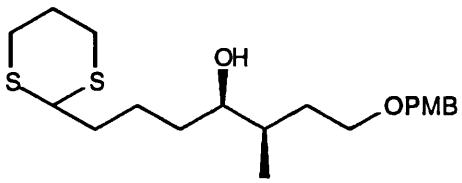
235

δ_H (400 MHz, $CDCl_3$) 7.38-7.15 (15H, m, *Ph*), 5.61 (1H, d, *J* 4.4 Hz, H6 or H7), 5.20 (1H, d, *J* 4.4 Hz, H6 or H7), 4.85 (1h, dd, *J* 6.4 Hz and 4.4 Hz, H3), 4.47 (2H, s, $PhCH_2OCH_2$), 4.45 (1H, d, *J* 11.2 Hz, $PhCH_2OCH_2$), 4.34 (1H, d, *J* 11.2 Hz, $PhCH_2OCH_2$), 4.32 (1H, d, *J* 11.7 Hz, $PhCH_2OCH_2$), 4.24 (1H, d, *J* 11.7 Hz, $PhCH_2OCH_2$), 3.97 (1H, d, *J* 10.2 Hz, $PhCH_2OCH_2$ @C4 or C5), 3.77 (1H, d, *J* 10.2 Hz, $PhCH_2OCH_2$ @C4 or C5), 3.64 (1H, dd, *J* 10.2 Hz and 4.4 Hz, $PhCH_2OCH_2$ @C3), 3.51 (1H, s, 5-O*H*), 3.41 (2H, s, $PhCH_2OCH_2$ @C4 or C5), 2.11 (3H, s, O*Ac*), 1.95 (3H, s, O*Ac*), 1.46 (3H, s, C1'-CH_3); δ_C (100MHz, $CDCl_3$) 169.8, 169.6, 138.1, 137.4, 137.0, 128.6, 128.4, 128.3, 128.3, 128.1, 128.0, 128.0, 127.7, 127.6, 106.0, 85.5, 77.4, 73.9, 73.8, 73.3, 73.1, 71.6, 69.9, 68.1, 67.5, 65.6, 20.9, 20.8, 20.6.



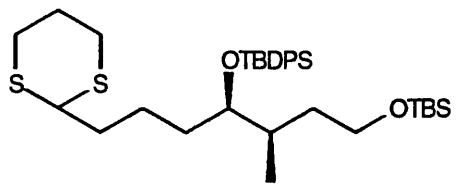
263

ν_{max}(film) 3069, 2931, 2856, 1589, 1471, 1454, 1427, 1360, 1199, 1110, 1006, 822, 739, 701, 665 and 612 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.72-7.62 (4H, m, SiPh), 7.46-7.21 (11H, m, Ph), 4.39 (2H, s, PhC*H*$_2$OCH$_2$), 3.76 (1H, dt, *J* 8.6 Hz and 2.6 Hz, CH$_2$C*H*(OSi)CH(CH$_3$), 3.39 (1H, dd, *J* 9.2 Hz and 6.3 Hz, one of CHC*H*$_2$I), 3.22 (2H, t, *J* 6.3 Hz, PhCH$_2$OC*H*$_2$), 3.09 (1H, dd, *J* 9.2 Hz and 7.9 Hz, CHC*H*$_2$I), 1.99-1.81 (1H, m, CH(OSi)C*H*(CH$_3$)C*H*$_2$I), 1.50-1.05 (6H, m, PhCH$_2$OCH$_2$C*H*$_2$C*H*$_2$C*H*$_2$), 1.04 (9H, s, ^tBu), 1.01 (3H, d, *J* 6.9 Hz, CH(OSi)CH(C*H*$_3$)).



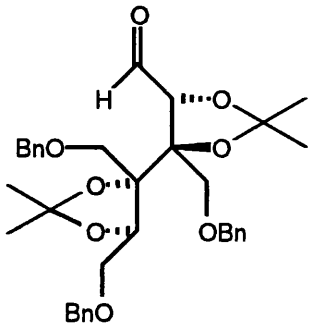
287

ν_{max}(film) 3416, 2932, 2851, 1611, 1512, 1461, 1421, 1364, 1301, 1247, 1173, 1089, 1033, 820 and 666 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.26 (2H, d, J 8.4 Hz, *Ar*), 6.88 (2H, d, J 8.4 Hz, *Ar*), 4.44 (2H, s, ArC*H*$_2$OCH$_2$), 4.05 (1H, t, J 6.9 Hz, CH$_2$SC*H*SCH$_2$), 3.81 (3H, s, ArOC*H*$_3$), 3.58-3.50 (2H, m, one of ArCH$_2$OC*H*$_2$ and CH$_2$C*H*(OH)CH(CH$_3$)CH$_2$), 3.48-3.42 (1H, m, ArCH$_2$OC*H*$_2$) 2.92-2.79 (4H, m, -C*H*$_2$SCHSC*H*$_2$CH$_2$-), 1.91-1.81 (1H, m, -C*H*$_2$SCHSC*H*$_2$CH$_2$-), 1.80-1.36 (9H, m), 0.86 (3H, d, *J* 6.5 Hz, CH(OSi)CH(C*H*$_3$)CH$_2$); δ_C (125 MHz, $CDCl_3$) 159.2 (s), 130.1 (s), 129.4 (d), 113.8 (d), 74.0 (d), 72.7 (t), 68.0 (t), 55.3 (q), 47.5 (d), 36.1 (d), 35.5 (d), 33.6 (t), 30.5 (t), 26.0 (t), 23.6 (t), 13.3 (q).



288

ν_{max}(film) 3070, 2930, 2894, 2856, 1471, 1426, 1388, 1360, 1255, 1110, 1048, 1006, 834, 775, 740, 702, and 665 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.69-7.65 (4H, m, SiPh), 7.43-7.34 (6H, m, SiPh), 3.75 (1H, t, *J* 7.0 Hz, CH_2S C*H*SCH_2), 3.58-3.50 (3H, m, C*H*(OSi)CH(CH_3)CH_2 and C*H*$_2$OTBS), 2.82-2.73 (4H, m), 2.10-2.04 (1H, m), 1.77-1.64 (3H, m), 1.48-1.29 (7H, m), 1.04 (9H, m, $SiPh_2{}^tBu$), 0.87 (9H, s, ^tBu), 0.85 (3H, d, *J* 6.8 Hz, CH(OSi)CH(C*H*$_3$)CH_2).



303

δ_H (500 MHz, $CDCl_3$) 9.60 (1H, s, C*H*O), 7.33-7.20 (13H, m, *Ph*), 7.15-7.13 (2H, m, *Ph*), 4.83 (1H, s, C*H*CHO), 4.64-4.58 (2H, m, includes 4.62 (1H, d, *J* 12.4 Hz, one of PhC*H*$_2$OCH_2 and PhCH_2OCH_2C*H*), 4.44 (1H, d, *J* 12.4 Hz, PhC*H*$_2$OCH_2), 4.33 (2H, s, PhC*H*$_2$OCH_2), 4.21 (2H, s, PhC*H*$_2$OCH_2), 3.97 (1H, dd, *J* 10.9 Hz, and 3.0 Hz, PhCH_2OC*H*$_2$CH), 3.68 (1H, d, *J* 9.9 Hz, PhCH_2OC*H*$_2$), 3.65 (1H, dd, *J* 10.9 Hz and 7.7 Hz, PhCH_2OC*H*$_2$CH), 3.56 (2H, s, PhCH_2OC*H*$_2$), 3.37 (1H, d, *J* 9.9 Hz, PhCH_2OC*H*$_2$), 1.52 (3H, s, C*H*$_3$), 1.43 (6H, s, 2x C*H*$_3$), 1.42 (3H, s, C*H*$_3$).

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145. See Table 8, Chapter 2 for derivatives and results.